1967

The Chemistry of Tertiary Amides and Related Compounds.

Kalil Phillip Ieyoub
Louisiana State University and Agricultural & Mechanical College

THE CHEMISTRY OF TERTIARY AMIDES AND RELATED COMPOUNDS

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor of Philosophy

in

The Department of Chemistry

by
Kalil Phillip Ieyoub
B.S., McNeese State College, 1958
M.S., Louisiana State University, 1965
January, 1967

ACKNOWLEDGMENT

The author wishes to express his sincere appreciation for the guidance given him by Dr. Paul E. Koenig who planned and directed this investigation. He also wishes to express his gratitude to Dr. J. L. E. Erickson and to Dr. G. E. Risinger for their interest in the author as a student and a friend, and for their many helpful suggestions.

The financial assistance in support of this research by Louisiana State University, Cities Service Corporation, and the National Science Foundation is gratefully acknowledged. The author wishes to acknowledge the financial assistance in the publication of this dissertation from the Dr. Charles E. Coates Memorial Fund of the L.S.U. Foundation donated by George H. Coates.

Finally, he would like to express his gratitude to his family and to his wife for their constant encouragement throughout his graduate career.

TABLE OF CONTENTS

PAGE

ABSTRACT

CHAPTER

I. INTRODUCTION 1

II. HISTORICAL PART 2

III. DISCUSSION 14

IV. EXPERIMENTAL PART 42

A. Preparation of Tribenzamide 42

B. Reaction of Tribenzamide and Grignard Reagents 43

C. Reduction of Tribenzamide 43

D. Alcoholysis of Tribenzamide 48

E. Reaction of Tribenzamide and Diazomethane . . 48

F. Reaction of Tribenzamide and Sulfuric acid . . 49

G. Bromination of Tribenzamide 50

H. Pyrolysis of Tribenzamide 50

I. Friedel and Crafts Reaction 51

J. Reaction of Tribenzamide and Methyl Iodide . . 51

K. Reaction of Tribenzamide and Amines 52

L. Reaction of Tribenzamide and Phenylhydrazine . 53

M. Ammonolysis of Tribenzamide 53

N. Reaction of Tribenzamide with Benzoyl Chloride 54

O. Attempted Reaction of Aldehydes with Tribenzamide 54

P. Attempted Synthesis of a Bicyclic Tertiary Amide 55

Q. Attempted Synthesis of Antimony and Arsenic Analogs of Tribenzamide 60

V. SUMMARY 62

VI. REFERENCES 64

VITA 68

ABSTRACT

A study has been made of the chemistry and the stereochemistry of tertiary amides, using tribenzamide as a representative tertiary amide. Tribenzamide was synthesized by a new method in which ammonia gas was bubbled through a 25% solution of benzoyl chloride in dry pyridine at room temperature. The reactions of tribenzamide with various reagents have been investigated.

Tribenzamide reacted with Grignard reagents in much the same way that esters and primary amides do. With phenylmagnesium bromide, triphenylcarbinol was obtained in 50% yield. Aliphatic Grignard reagents with tribenzamide yield ketones. With methylmagnesium bromide, acetophenone was produced in 36% yield; ethylmagnesium bromide yielded ethyl phenyl ketone in 43% yield; hexyl magnesium chloride yielded hexyl phenyl ketone in 20% yield. An attempt was made to react t-butylmagnesium bromide with tribenzamide. The product obtained was a brown, extremely viscous oil which could not be distilled or recrystallized.

An attempt was made to reduce tribenzamide to the corresponding tertiary amine. Reduction with lithium aluminum hydride yielded N-benzylbenzamide and benzyl alcohol in 32% yield. With lithium diethoxyaluminohydride, N-benzylbenzamide and benzaldehyde were produced in 90% yield; zinc and acetic acid yielded N-benzylbenzamide in 84% yield; diborane reduction and sodium borohydride

reduction also yielded benzyl alcohol and N-benzylbenzamide. An attempt to reduce tribenzamide with sodium in ethanol resulted in benzamide and ethyl benzoate by virtue of nucleophilic attack by the ethoxide ion on a carbonyl carbon of tribenzamide, followed by cleavage. Similarly, an attempted Clemmensen reduction of tribenzamide yielded benzoic acid and dibenzamide by attack of the chloride ion on a carbonyl carbon followed by cleavage. Hydrogen in the presence of a catalyst failed to reduce tribenzamide.

A number of other reactions involving nucleophilic attack at the carbonyl carbon of tribenzamide were performed. Hydrazine hydrate reacted with tribenzamide to yield sym-dibenzoylhydrazine; phenylhydrazine produced benzoic acid phenylhydrazide in 62% yield; ammonia and tribenzamide yielded benzamide and dibenzamide; benzylamine reacted with tribenzamide to yield N-benzylbenzamide; ethylamine yielded dibenzamide and N-ethylbenzamide, pyridine produced dibenzamide and benzoic acid; o-phenylenediamine reacted with tribenzamide to yield 2- phenylbenzimidazole in 77% yield; diethylamine yielded a product which could not be purified well; diphenylamine did not react with tribenzamide.

Ethanolysis of tribenzamide produced ethyl benzoate and benzamide. Diazomethane reacted with tribenzamide to yield benzamide. It was expected that α-methoxyacetophenone would be produced, but this product was not isolated. Reaction of sulfuric acid and tribenzamide yielded benzoic acid rather than the desired tribenzoylammonium salt.

Bromination of tribenzamide yielded benzoic acid and dibenzamide. A Friedel-Crafts reaction between tribenzamide and benzene did not produce benzophenone as had been reported by other investigators. The product was benzoic acid.

Tribenzamide was pyrolyzed to yield benzonitrile and benzoic anhydride and a high-melting solid which was not identified.

Attempts to form quaternary salts of tribenzamide were unsuccessful. Neither methyl iodide nor p-bromophenacyl bromide could be made to react with tribenzamide.

On the basis of infrared and n.m.r. spectral studies, a pyramidal structure was assigned to tertiary amides.

The reaction of tribenzamide with benzoyl chloride yielded benzoic acid and dibenzamide. Tribenzamide did not react with aldehydes.

The results of an attempt to synthesize a bicyclic tertiary amide are presented, as well as the results of an attempt to prepare the arsenic and antimony analogs of tribenzamide.

INTRODUCTION

Remarkably little research has been done in the past concerning the chemistry of the class of compounds known as tertiary amides $(R\text{-}CO)_3N$. Probably a major reason for this lack of information is the fact that tertiary amides are, in general, extremely difficult to prepare. Noller[1] stated as late as 1954 that tertiary amides did not exist, although he later corrected his statement.[2] Actually, tribenzamide $(C_6H_5CO)_3N$ had been prepared in 1893[3]; and triacetamide, first reported in 1870[4], was probably actually prepared for the first time in 1890.[5] N-Acylphthalimides are well known, and have been employed as derivatives for the characterization of acyl halides.[6] Thompson[7] prepared a number of tertiary amides in 1951 by direct diacylation of primary amides.

Work in this laboratory has shown that tertiary amides have a characteristic absorption at 5.85μ, the location of the aldehydic and ketonic carbonyl.[12,27a] It is, therefore, of great interest to learn whether tertiary amides undergo reactions typical of true carbonyl compounds, in contrast to the behavior of primary amides and other carboxylic chalcogen derivatives.

Spectral studies and the chemical and physical properties of the tertiary amides raise some very interesting questions concerning the structure of these compounds. The goal of the present investigation was the determination of the chemical behavior and structure of tertiary amides and related compounds. The carbonyl system, whether ketonic or amide-like, should and does undergo reactions with nucleophilic reagents including Grignard reagents, amines, alcohols, hydrazines and bases, as well as with reducing agents and other reagents. A number of these reactions were investigated and the results are reported herein.

HISTORICAL PART

General

A careful search of the literature from 1809 to the present yielded relatively few references to tribenzamide or other tertiary amides. Most of these references dealt only with the preparation of these compounds and not with their chemistry.

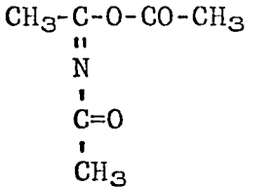
It should be pointed out that there may exist some confusion regarding nomenclature of tertiary amides. Brown and others[8] regard as tertiary amides compounds of the formula $R-CO-NR'_2$. The author of this dissertation prefers to regard the above class of compounds as N,N-dialkylamides, which indicates that they are merely N-alkylated primary amides. Almost all of the literature references mentioned in this dissertation consider compounds of the structure $(R-CO)_3N$ to be tertiary amides, and this system of nomenclature, approved by the IUPAC, will be used here.

The simplest known member of the tertiary amide series is triacetamide, first reported in 1870 by Wichelhaus[4], who heated acetic anhydride with acetonitrile and obtained a product melting at 78°-79°; although his yields were low, the reaction has been cited several times[9] as a general method of synthesis of tertiary amides.

A subsequent investigator studied the reaction of the sodium salt of diacetamide with acetyl chloride, and also obtained a low yield of a material melting at 77° [10]. More recently, triacetamide was prepared by Kocheshkov[11] by reaction of ketene with diacetamide; a melting point of 8° was reported, with the comment that repeated attempts to

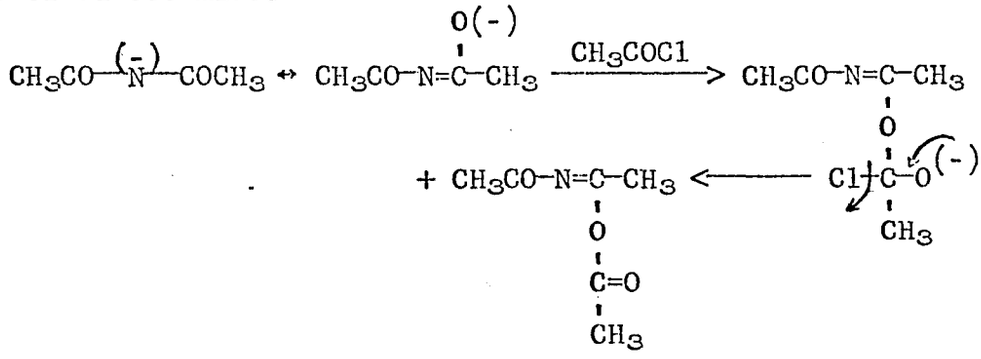
duplicate Wichelhaus' work led instead to diacetamide with a melting point of 78°. Work in this laboratory[12] has substantiated Kocheshkov's observation of the melting point of triacetamide. Bell[12] obtained his product by the reaction of diacetamide and isopropenyl acetate, and found the melting point to be 8°. He was unable to duplicate Wichelhaus' results.

It is now clear that triacetamide was most probably first prepared by Hentschel[5] from acetic anhydride and diacetamide, and was subsequently obtained by Brunner[13] from potassium cyanate and acetic anhydride. In view of the work of Wichelhaus, Brunner proposed that his compound, which melted at 8°, had the following structure:

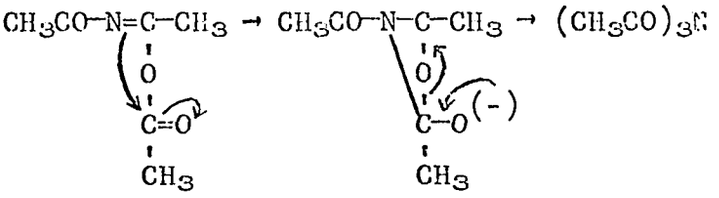


However, the work of Kocheshkov[11] and observations in this laboratory support the triacylamine structure.

It is quite likely that Wichelhaus[4] and Rakshit[10] actually prepared the isomeric imidoester shown above. Wichelhaus' method could understandably have given the indicated structure, as could Rakshit's if O-acylation is favored over N-acylation in the ambident sodio derivative of diacetamide.



Kocheshkov[11] suggests that the imidoester structure is an intermediate in his preparation of triacetamide; thus he believes that ketene reacts with the lactim (imide) form of diacetamide, but that the resulting O-acyl structure immediately tautomerizes to the tertiary amide.



Except for five mixed aliphatic tertiary amides prepared by Kocheshkov[11], no other purely aliphatic representatives of this class of compounds have been reported.

Aromatic tertiary amides are somewhat better known, tribenzamide being mentioned more often than other tertiary amides in the literature. Tribenzamide was first prepared in 1890 by Curtius[3], by the reaction of benzoyl chloride with benzamide. In 1893, Jaffe[14] reported tribenzamide to be a side product in the preparation of benzamide by the action of ammonium carbonate on benzoyl chloride. Wheeler[15], in 1898, prepared tribenzamide by reaction of acetobenzimidoethylic ether and benzoyl chloride at temperatures of 100°-120°. In the same year, Blacher[16] reported a preparation of tribenzamide; he reacted benzoyl chloride with a suspension of sodium benzamide in xylol. Brunner[13] obtained small yields of tribenzamide, benzonitrile, and dibenzamide by reaction of benzoic anhydride with potassium cyanate.

In 1910, Garrod and Hurtley[17] treated urine with benzoyl chloride and thought they had isolated a benzoyl-tryptophane derivative, possibly benzoylkynurine, but Ellinger and Riesser[18] showed that the product of this reaction was tribenzamide.

Tribenzamide is not mentioned again in the literature until 1928, when Parts[19] reported that the heat of combustion of tribenzamide was 2425.5 Kcal/mole.

Yasumura[20], in 1951, reported the preparation of tribenzamide by the hydrolysis of benzyl (sic) chloride with ammonium hydroxide. Thompson[7] obtained tribenzamide in high yield by the direct diacylation of benzamide with benzoyl chloride after complexing the latter with pyridine.

Blanchard[21], in 1961, obtained tribenzamide as one product in the reaction of lithium nitride and benzoyl chloride in diethylene glycol dimethyl ether. In 1960, Farrar[22] prepared tribenzamide by reacting 2,4,5-trichlorobenzenesulfonyl chloride and dibenzamide in pyridine at 100° for twenty-four hours. Recently[23], the synthesis of tris(m-trifluoromethyl)tribenzamide was reported in the literature.

Reactions of Tertiary Amides

There exist only fragmentary data in the literature on the chemical behavior of the tertiary amides. Curtius[3] reported that tribenzamide sublimes undecomposed, and that it is cleaved by sodium hydroxide to give ammonia and sodium benzoate. Brunner[13] noted the facile hydrolysis of triacetamide. Kocheshkov[11] reported (without explicit experimental data) that triacetamide "easily acetylates water, alcohols, amines, acetic acid and acetamide," that all three acyl groups are equivalent in the sense that any one of the three will participate in acylation reactions (supporting the triacylamine structure), and that the aliphatic tertiary amides generally react as do acid anhydrides, e.g., will undergo trans-acylation and will produce ketenes on being heated. Tyka[24] has employed triacetamide and N-acetyldibenzamide in

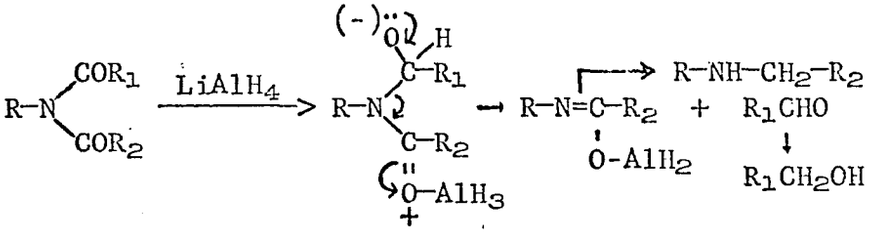
Friedel-Crafts acetylations of benzene. He also carried out a Friedel-Crafts reaction with tribenzamide and benzene and claimed that the product was benzophenone. No other reference to the chemical behavior of tertiary amides is made in the literature.

Tertiary amides should undergo several reactions. The present investigation was concerned primarily with reactions of the carbonyl group(s); related work includes the following:

Reduction Reactions

While no mention of direct reduction of tertiary amides can be found in the literature, several references are given to reduction reactions analogous to those which might be expected of tertiary amides.

Witkop and Patrick[25], in 1952, reported the formation of alkylamines when lithium aluminum hydride was used to reduce secondary amides:



In 1961, Schreiber and Fernandez[26] reported the lithium aluminum hydride reduction of N-alkyl- and N-phenylsuccinimides to N-substituted-pyrrolidines, and in some cases, to both the substituted pyrrolidines and to amino alochols. The latter reaction was observed in the reduction of N-benzhydryl-, N-t-butyl-, and N-phenylsuccinimides. These authors were also successful in reducing succinamic acids by use of lithium aluminum hydride.

Work in this laboratory[12,27a,b] on the reduction of tertiary amides is the first such work reported. Reduction using lithium

aluminum hydride as the reducing agent produced a product identified as N-benzylbenzamide. This reduction was thus analogous to that reported for secondary amides.

In 1958, Brown and Rao[28] synthesized aldehydes by reduction of acid chlorides by lithium tri-t-butoxyaluminohydride. They state that the introduction of alkoxy substituents into lithium aluminum hydride moderates the reducing capacity of this reagent. Aldehydes were obtained in high yields by the following reaction:

$$RCOCl + LiAlH[OC(CH_3)_3]_3 \rightarrow RCHO + Al[OC(CH_3)_3]_3$$

It seems likely that the carbonyl group of the tertiary amide might undergo a reduction similar to that described for acid chlorides, since the dibenzamide anion has been found to act much like the chloride ion in the facility with which it is cleaved from the molecule.

Brown and Tsukamoto[8], in 1959, applied a similar reduction to N,N-dimethylamides. Again, they obtained high yields of aldehydes by use of lithium diethoxyaluminohydride as a selective reducing agent. This hydride is easily prepared by reacting lithium aluminum hydride and ethyl acetate on a mole-to-mole basis or by reacting two moles of ethyl alcohol with one mole of lithium aluminum hydride.

In 1959, Zakharkin and Khorlina[29] synthesized aldehydes by the reduction of dialkylamides with diisobutylaluminum hydride. These same authors, in 1962, reported the reduction of esters to aldehydes using the same hydride as the reducing agent.[30]

Tyka[24] reduced the phosphorus analog of tribenzamide using lithium aluminum hydride and obtained benzyl alcohol and a small amount of $(C_6H_5CHOH)_3P$.

Prior to investigations in this laboratory[27a], no work had been done on the reduction of tertiary amides.

Diborane has been used extensively in recent years as a reducing agent. In 1960, Brown and Rao[31] employed diborane in the reduction of a number of representative organic compounds, including carboxylic acids, aldehydes, esters, and ketones to alcohols, and in the reduction of nitriles to amines. N-Alkyl- and N,N-dialkylamides were reduced rapidly under relatively mild conditions by the use of diborane.[32] In all cases the amides were reduced to the corresponding amines in high yields.

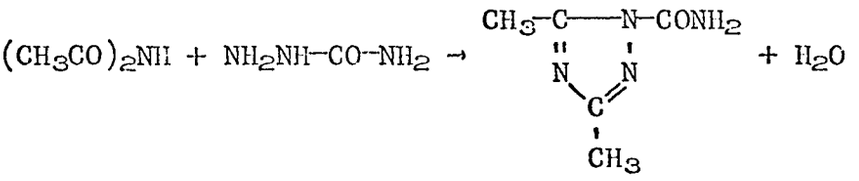
Cowart[27b] employed diborane as a reducing agent in an attempt to convert 4,4',4"-trichlorotribenzamide to the corresponding amine. One of the products he obtained was N-(chlorobenzyl)-p-chlorobenzamide, the same product as that obtained from the lithium aluminum hydride reduction. Another product obtained was not identified.

Sodium borohydride is another reagent which has recently been employed as a very effective reducing agent. Chaikin and Brown[33] found that sodium borohydride in water or methyl alcohol is effective in reducing aldehydes and ketones to the corresponding alcohols. They found, also, that sodium borohydride in dioxane or diethyl carbitol would reduce acyl chlorides, but that carboxylic acids and acid anhydrides show only slight reduction on prolonged heating; esters and nitriles were virtually unaffected.

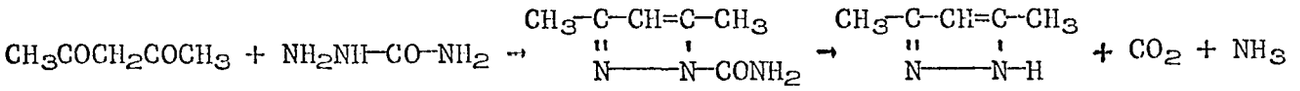
In 1961, Dale[34] reduced acyclic 1,3-diketones to the corresponding 1,3-diols in excellent yields by the use of sodium borohydride. In the same year, sodium borohydride was employed as a reducing agent in the reduction of phthalimides to hydroxyphthalimidines.[35]

Hydrazine Reactions

In 1915, Brunner[36] reacted secondary amides with hydrazine and obtained substituted triazoles. Similarly, he reacted diacetamide with semicarbazide and obtained a cyclic compound[36]:

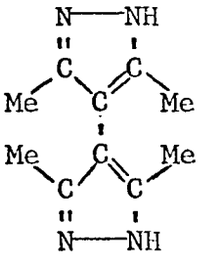


Brunner also reacted acetylacetone and semicarbazide as follows:

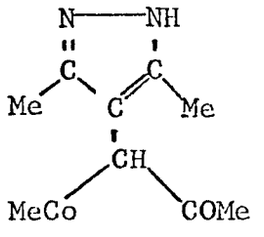


In the following year, Wolchowe[37] reported that the reaction of dibenzamide and phenylhydrazine hydrochloride yielded 1,3,5-triphenyl-1,2,4-triazol.

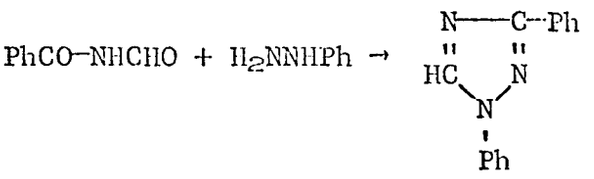
In 1957, Mosby[38] reported that the reaction of 3,4-diacetylhexane-2,5-dione and excess hydrazine yielded a cyclic compound,



while a single equivalent of hydrazine yielded



Thompson[7] has reported the reaction of N-formylbenzamide and phenylhydrazine to proceed as follows:



Work in this laboratory has shown that tertiary amides react with hydrazine in quite a different manner.[12,27a,b] Rather than forming the expected triazoles, they gave symmetrical diacylhydrazines. As discussed on page 21 of this dissertation, it might well have been expected that tertiary amides would be excellent acylating agents because of steric hindrance about the nitrogen. Tribenzamide was reacted with a variety of amines as part of this investigation in order to test the acylating ability of tertiary amides.

Grignard Reactions

Maxim[39] reports that the reaction of primary amides and Grignard reagents yields only ketones.

In 1955, Heyns and Pyrus[40] reported that amides, R—CO—NH—R′, in three to five fold excess of Grignard reagent, produce a ketone and a primary amine.

Bouveault[41] had earlier investigated the reaction of Grignard reagents and disubstituted formamides and found that an aldehyde and a secondary amine were produced.

Grignard and Tissier[42] reported work with acid anhydrides, which could possibly react in much the same manner as do tertiary amides. These authors showed that tertiary alcohols could be obtained from the reaction of anhydrides and Grignard reagents.

Newman and Smith[43] showed that the first step in this reaction was the formation of ketone, and that the ketone could be isolated under certain experimental conditions.

Mustafa[44] has obtained triphenylcarbinol and benzanilide by the reaction of phenylmagnesium bromide and N,N-dibenzoylaniline. He also reacted phenylmagnesium bromide with benzanilide to obtain benzophenone anil.

In 1963, Tyka[24] reported the preparation of triphenylcarbinol when he reacted tribenzoylphosphine with phenylmagnesium bromide; however, with α-$C_{10}H_7MgBr$, he obtained only α-$C_{10}H_7COC_6H_5$.

These references describe the closest analogies that can be drawn to the reactions of tertiary amides, with the possible exception of an article by Grignard[45] himself, who, in 1901, reported that carboxylic esters react with Grignard reagents to yield trialkylcarbinols.

Kharasch[46] makes the statement that some carboxylic esters with Grignard reagents yield ketones, although it has not been demonstrated that these ketones are present prior to hydrolysis.

Earlier work in this laboratory has shown that aromatic Grignard reagents react with tertiary amides to yield tertiary alcohols, while aliphatic Grignard reagents react with tertiary amides to yield ketones.[12,27a,b] Since it was postulated that steric requirements of the initial adduct determines which type of product is formed, it is of interest to perform the reaction using a large aliphatic Grignard reagent such as t-butylmagnesium bromide.

Alcoholysis and Ammonolysis

Only recently has alcoholysis of a tertiary amide been performed.[27b] By reacting ethanol with 4,4',4''-trichlorotribenzamide, Cowart obtained

the expected ester and p-chlorobenzamide, contaminated with secondary amide, by nucleophilic attack by the ethoxide ion on a carbonyl carbon, followed by cleavage and formation of the ester and the secondary amide. A similar result was obtained by Tyka[24] when he reacted tribenzoylphosphine with ethanol.

It has long been known that esters can be prepared by reacting anhydrides with alcohol. Reid[47], in 1909, carried out alcoholysis of benzamide and the nitrobenzamides, using hydrochloric acid as a catalyst. He found, predictably, that the amides were converted to the corresponding esters.

Acid anhydrides, when treated with ammonia, are converted to primary amides and ammonium salts.[48]

The only reported ammonolysis was carried out recently on tertiary amides.[12,27b] The expected products, primary amide and secondary amide, were obtained:

$$(R\text{—}CO)_3N + NH_3 \rightarrow R\text{—}CONH_2 + (R\text{—}CO)_2NH$$

Ammonolysis of tribenzoylphosphide also yielded benzamide.[24]

Diazomethane Reaction

Labruto[49] reacted diazomethane with phthalimide and obtained N-methylphthalimide. In similar fashion, succinimide and diasomethane gave N-methylsuccinimide.

In 1935, Irrera[50] obtained N-methylglutarimide from the reaction of diazomethane and glutarimide, and N-methyldiphenimide from diphenimide and diazomethane.

Since an analogous reaction at the nitrogen of tertiary amide compounds seems impossible, it is of interest to note whether diazomethane

would attack the carbonyl carbon of tribenzamide if indeed it would react at all.

Bromination and Reaction with H_2SO_4

Tyka[24] performed reactions with $(C_6H_5CO)_3P$ which furnished results closely associated with the results of the similar reactions using tertiary amides as the substrate.

In 1963, he reacted $(C_6H_5CO)_3P$ with three molar equivalents of bromine and obtained three molar equivalents of benzoyl bromide and one molar equivalent of phosphorus tribromide.

In the same year, he described the reaction between $(C_6H_5CO)_3P$ and sulfuric acid:

$$(C_6H_5CO)_3P + H_2SO_4 \rightarrow PH_3 + 3C_6H_5COOSO_3H$$
$$\downarrow$$
$$3C_6H_5COOH + 3H_2SO_4$$

These transformations were performed as part of this investigation using tribenzamide instead of tribenzoylphosphine as the substrate.

Pyrolysis

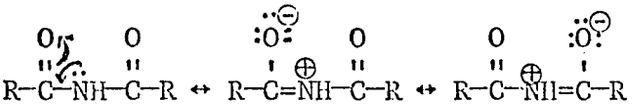
Curtius[3] reported that tribenzamide sublimed undecomposed. In this laboratory, heating of tribenzamide led to pyrolysis rather than sublimation.

DISCUSSION

General

An important aspect of the study of the chemistry of tertiary amides is the difficulty with which these compounds are prepared. The aroyl groups are not easily placed around the nitrogen atom in molecular models because of steric factors. This difficulty is less significant in secondary amides which possess only two large groups on the nitrogen atom, and therefore, are not sterically unfavored.

Also, the stability of primary and secondary amides is probably enhanced by resonance.



The addition of a third aroyl group on the nitrogen atom may inhibit such resonance in tertiary amides since coplanarity becomes sterically unfavored.

Probably the best method for synthesis of aromatic tertiary amides is the method used by Thompson.[7] He produced tribenzamide by reacting benzoyl chloride and benzamide in pyridine using chloroform as the solvent. Thompson is convinced that the tertiary amide is formed as a result of direct diacylation of benzamide by the benzoyl chloride, since dibenzamide and benzoyl chloride did not react under the same experimental conditions to yield tribenzamide.

It is interesting to note that Thompson[7] makes the statement that diacylation in the ammonia system was limited to primary amides. He further stated that ammonia, as well as several amines, yielded only the corresponding substituted benzamides as the primary acylation

product. A portion of this investigation was concerned with attempts to synthesize tertiary amides by facile, feasible methods. It was found that tribenzamide could be synthesized easily, although in only 20% yield, by simply bubbling ammonia through a solution of benzoyl chloride (25%) and pyridine (75%) at room temperature.

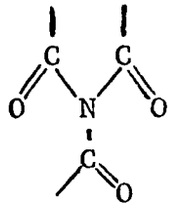
This method was first employed by Tyka[24] in the synthesis of $(C_6H_5CO)_3P$. He simply bubbled PH_3 through a solution of benzoyl chloride (25%) and pyridine (75%) at room temperature and obtained the product by precipitating it upon the addition of water to the reaction mixture.

From a product yield standpoint, this method can not compare with the method of synthesis employed by Thompson. However, it is interesting in that the result of this method is a direct contradiction of the statement made by Thompson.

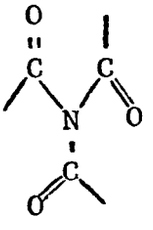
Structure

The infrared and n.m.r. spectra and the chemical and physical properties of the tertiary amides raise some very interesting questions concerning the structure of these compounds; several possibilities present themselves.

In primary amides the $-CO-N=$ system is planar.[51] If one assumes a planar (sp^2) nitrogen atom in the tertiary amides then two configurations are possible:



syn

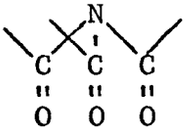


anti

But Bell[12] has shown that the n.m.r. spectrum of triacetamide has a single peak, thus indicating the equivalency of all the hydrogen atoms. A single carbonyl absorption in the infrared spectrum of triacetamide supports the theory that all three carbonyl groups are equivalent. Therefore, the anti structure is the correct one -- if the nitrogen is in fact sp^2 hybridized. Actually, Dreiding models indicate some steric interference between methyl groups in the syn structure.

Reaction of tertiary amides with hydrazine is interesting in that the tertiary amides cannot assume the syn configuration corresponding to the trans-trans configuration[52] which dibenzamide must clearly favor and which would be highly favorable to the formation of the five-membered triazole ring. Hydrazine did not react with triacetamide or tribenzamide to yield cyclic triazoles; instead, hydrazinolysis occurred with both compounds to give the symmetrical diacylhydrazines.

A third possibility involves a pyramidal structure (sp^3 nitrogen) which might very properly be called a triacylamine:



In the case of diacetamide, the equivalents of the two planar structures shown above have been isolated and their infrared spectra studied.[52] It might be suggested that the 8° and 78° melting points reported for triacetamide represent different configurational isomers selected from the three possibilities shown. The steric interference in the syn structure would surely make it the least stable, if indeed it can exist at all; but isolation of the anti and pyramidal forms might be possible. This suggestion has not been supported by recent

work[12,27a,b] in this laboratory, where conversion of the 8° form to the 78° material was not effected by heating, cooling or prolonged standing. The analogous transformation to the higher melting form occurs readily enough with diacetamide.[52]

A somewhat different structural situation exists for the aromatic tertiary amides. Dreiding models of tribenzamide show clearly that the molecule cannot be planar in the syn structure shown above. A planar structure is feasible for the anti structure, though the models show about as much steric interference as is present in the planar configuration of the trityl cation or of benzophenone. Jones[53] has calculated an angle of about 39° between the planes of the benzene rings in benzophenone. Thus, while the planar anti structure may be possible, the syn structure can only exist if the phenyl rings are twisted out of plane. Maximum π interaction between the carbonyls and the benzene rings would require rotation about the C–N single bond; then, however, there is little reason for the nitrogen atom to be sp^2 hybridized (with a pair of non-bonding electrons in the p orbital), and it would presumably revert to the sp^3 state.

Primary amides, which are known to be planar, have a carbonyl absorption at 6.0 μ, slightly shifted from the carbonyl peak of a tertiary amide. This leads to the conclusion that the carbonyl group of primary amides does not possess the same characteristics as the carbonyl groups of a tertiary amide. It is possible that this nonequivalency in carbonyl characteristics is brought about by a difference in the stereochemistry of tertiary and primary amides. If this assumption can be made, then it can be said that tertiary amides are not planar as are primary amides, but are pyramidal.

Like triacetamide, the aromatic tertiary amides (other than N-benzoylphthalimide) which were examined in this laboratory show only a single infrared carbonyl absorption. Thus, the carbonyl groups must be symmetrically oriented, and the two structural possibilities for tertiary amides are the planar anti configuration or the pyramidal model. The pyramidal arrangement is favored by observation in this laboratory that tribenzamide has a permanent dipole moment.[54]

Several observations do not support the suggestion that tertiary amides possess a pyramidal structure.

It was expected that tertiary amides, having the triacylamine structure, might form quaternary salts as do tertiary amines. However, tribenzamide failed to react with methyl iodide. Had the tertiary amide undergone N-methylation, the pyramidal structure would have been strongly indicated. Failure to react with methyl iodide does not especially rule out the pyramidal structure, however, since the nucleophilicity of the nitrogen would be strongly diminished even by inductive interactions of the carbonyls. p-Bromophenacyl bromide was also heated with tribenzamide in an effort to achieve quaternization of the tertiary amide nitrogen. Only unreacted tribenzamide was obtained.

Another piece of evidence which does not favor the assignment of the triacylamine structure to tertiary amides is the lack of success in reducing tertiary amides to the corresponding tertiary amines. In all cases, reduction gave totally unexpected results.

Probably there would be little C=N double bond character in either of the two possible configurations (planar or pyramidal N) though the bond order would certainly be higher in the planar molecule than in the pyramidal structure. Correspondingly, the infrared carbonyl absorption

should, and does, appear in the vicinity of that of aldehydes and ketones. All of the tertiary amides thus far investigated in this laboratory show a strong absorption at 1230-1260 cm^{-1}, in the region of the "imide III" band assigned by Uno and Machida[52] to C–N–C antisymmetric stretching with a contribution from N–H in-plane deformation. The N–H contribution is, of course, impossible for the tertiary amides. The characteristic absorption at about 1240 cm^{-1} is almost of necessity a C–N stretching absorption like that observed in the same vicinity for aromatic amines. (See Table I.)

Since all the acyclic tertiary amides studied thus far show the same spectral characteristics, their structures must be closely related; the C–N bonds, for example, must be the same in every case. It is, therefore, suggested that tertiary amides possess a pyramidal structure and are not coplanar molecules, at least in the cases studied thus far. This suggestion is based mainly on physical data such as spectral studies, dipole moment measurements and molecular model observations. As was stated, the fact that tertiary amides did not form quaternary nitrogen compounds and were not reduced to tertiary amines does not preclude the possibility that these compounds possess a pyramidal structure. It is possible that these reactions would occur under different conditions.

Reactions

From observations to date, tertiary amides react somewhat as do primary and secondary amides, with some marked differences. Hydrolysis and ammonolysis proceed remarkably rapidly in some cases; qualitatively, at least, the hydrolysis of triacetamide proceeds as rapidly in neutral

Table I. Characteristic Infrared Absorptions (cm^{-1}) of Tertiary Amides

	C=O	C–N
Triacetamide[a]	1725	1230
N-Benzoylphthalimide[b]	1700-1800[c]	1243, 1260
Tribenzamide[b]	1705	1245
3,3′,3″-Trimethyl-[d]	1695	1260
4,4′,4″-Trimethyl-[b]	1713	1253
4,4′,4″-Trimethoxy-[b]	1725	1230
4,4′,4″-Trinitro-[b]	1735	1230
4,4′,4″-Trichloro-[b]	1705	1240

(a) Neat liquid; (b) KBr disc; (c) 4 Peaks, strongest at 1738 cm^{-1}; (d) Nujol mull.

solution as does the hydrolysis of acetic anhydride, and is very much faster in the presence of a trace of acid. It is not surprising that triacetamide should be more reactive toward nucleophiles than is acetamide or even diacetamide, because of the greater electrophilicity of the carbonyl carbons in triacetamide, the steric requirements about the nitrogen atom, and the relative acidities of the leaving groups in the three cases. However, N-acetylphthalimide reportedly can be recrystallized successfully from boiling water.[55] It is difficult to see why such a compound would not be hydrolyzed at the N-acetyl bond even more readily than is triacetamide. Actually, prolonged digestion with boiling water opens the imide ring, to form N-acetylphthalamic acid, rather than attacking the acetyl group.[55] Angle strain in the imide ring may account for the observed reaction path.

Interestingly, too, tribenzamide is not readily affected by boiling water; furthermore, Thompson[7], in the course of his preparations, extracted chloroform solutions of various aromatic tertiary amides with 1 N hydrochloric acid and with 0.5 N sodium hydroxide solution, apparently without extensive hydrolysis of the tertiary amides.

The tertiary amide system should, and does, show interesting results when reacted with various reagents. A survey of some reactions of tribenzamide as a representative tertiary amide includes the following:

Tribenzamide Reduction

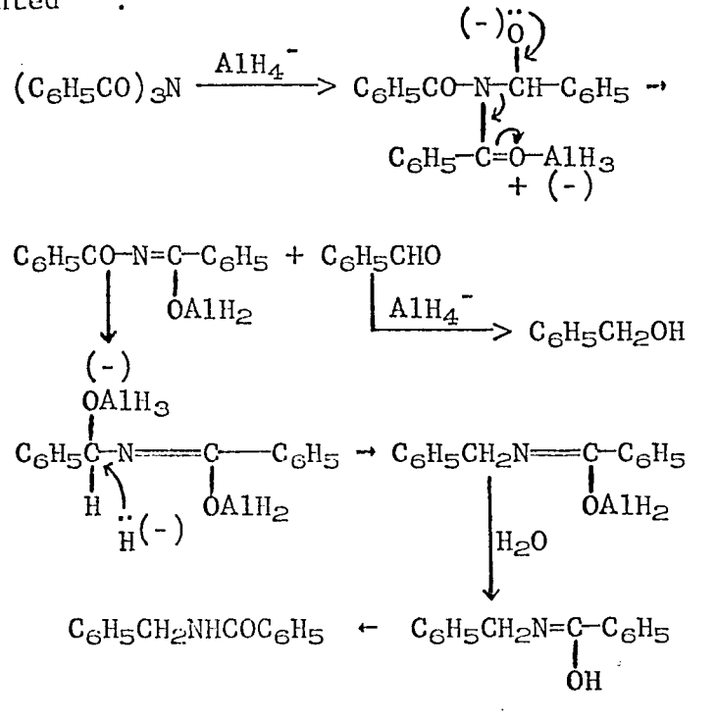
Reduction of tribenzamide to tribenzylamine was not achieved. The usual reduction methods, i.e., sodium and alcohol and zinc amalgamhydrochloric acid (Clemmensen reduction) appear to cleave the compound before reduction can occur. Benzamide and ethyl benzoate were obtained from

the sodium and alcohol reduction, and benzoic acid and dibenzamide were obtained from the attempted Clemmensen reduction. These products can be seen as arising from an attack on the carbonyl carbon by ethoxide ion in the sodium and alcohol reduction, and by an attack on the carbonyl carbon by the chloride ion in the Clemmensen reduction attempt.

It seemed likely that catalytic hydrogenation should have successfully reduced the compound since there was less likelihood of cleavage. However, the method did not prove to be effective at all; there was no reaction.

The powerful reducing agent, lithium aluminum hydride was used with surprising results. The expected lithium salt was produced, and gave, upon hydrolysis, relatively small yields of N-benzylbenzamide. The reaction was thus analogous to that reported for secondary amides[25], but it is at first glance surprising that the N-alkylamide was not reduced further, especially since a 3:1 mole ratio of lithium aluminum hydride to tribenzamide was employed.

A mechanism for this reduction and an explanation of the products have been presented[27b]:



In the second step of this mechanism, the electrons originally forming a C—N bond migrate toward the carbon attached to the positively charged oxygen atom. It is suggested that they are attracted toward this carbon because it has a greater positive charge than that residing on the carbonyl carbon of the benzoyl group.

No benzyl alcohol was isolated, but an infrared spectrum of the remaining oil from which the crystals of N-benzylbenzamide were filtered showed hydroxyl absorption.

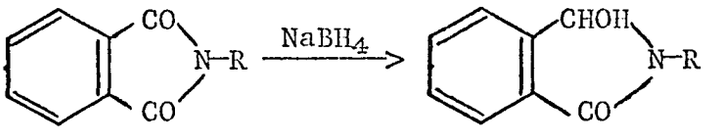
The chemistry of tertiary amides was shown to be similar to the chemistry of esters and ordinary amides when lithium diethoxyaluminohydride was used as a reducing agent. Brown and Tsukamoto[8] had earlier prepared aldehydes by reducing N,N-dimethylamides with lithium diethoxyaluminohydride. Zakharkin and Khorlina[29,30] had also prepared aldehydes in a similar manner; they reduced both dialkylamides and esters to aldehydes using diisobutylaluminum hydride as a reducing agent.

As might have been predicted, tribenzamide gave good yields of benzaldehyde upon reduction. The other product was identified as N-benzylbenzamide and was produced in 90% yield. The method of preparation of the diethoxyaluminohydride reducing agent appeared to have some effect on the yield of benzaldehyde. The yield was very small when ethyl acetate and lithium aluminum hydride were used to prepare the reagent; however, when ethyl alcohol and lithium aluminum hydride were used to prepare the reducing agent, high yields of benzaldehyde were obtained.

Diborane and sodium borohydride were employed as reducing agents for tribenzamide with the results being similar to those obtained by Cowart[27b], who obtained N-(p-chlorobenzyl)-p-chlorobenzamide and a

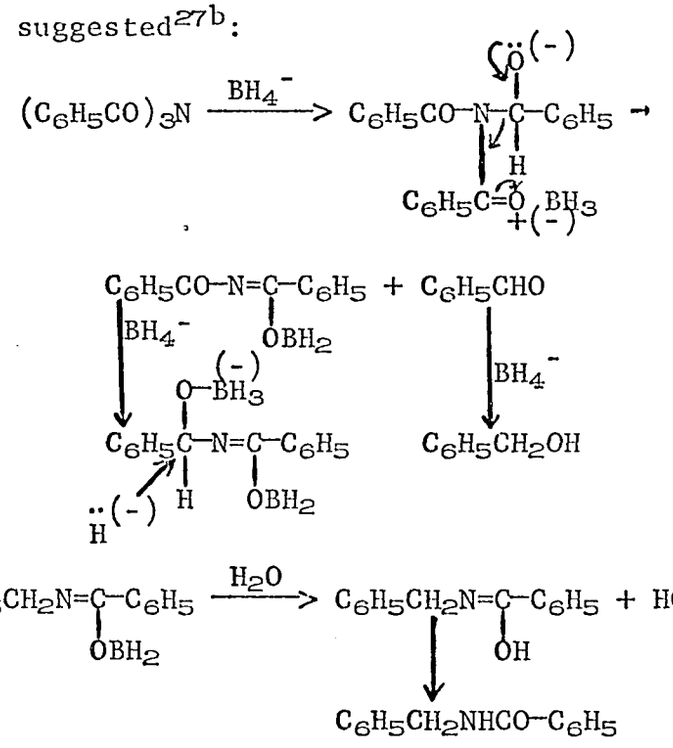
high-melting white solid from the reduction of 4,4',4''-trichlorotribenzamide with diborane.

N-Benzylbenzamide and benzyl alcohol were obtained from the reduction of tribenzamide. No other solid product was obtained. It was anticipated that sodium borohydride might be used to reduce tribenzamide in much the same manner that it was employed to reduce phthalimides to hydroxyphthalimidines.[35]



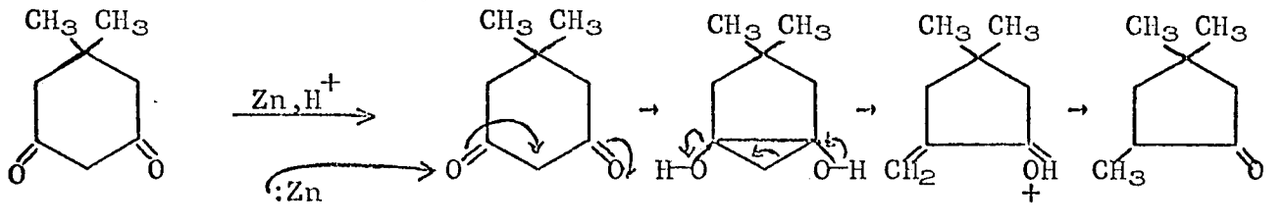
Various attempts were made to isolate a product similar to the above, using various experimental conditions, but the only product which could be isolated was N-benzylbenzamide.

A mechanism analogous to that of the lithium aluminum hydride reduction has been suggested[27b]:

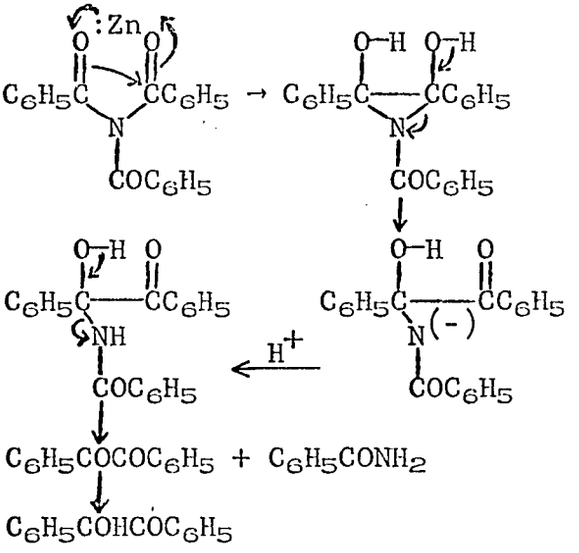


Tribenzamide was also reduced to N-benzylbenzamide using zinc dust and acetic acid as the reducing agent. It was speculated that this reduction might proceed in a manner similar to that described by Brewster[56],

who performed the following reaction using zinc and acetic acid as the reducing agent:



Applying an analogous mechanism to the tribenzamide reduction, the following sequence might be predicted:



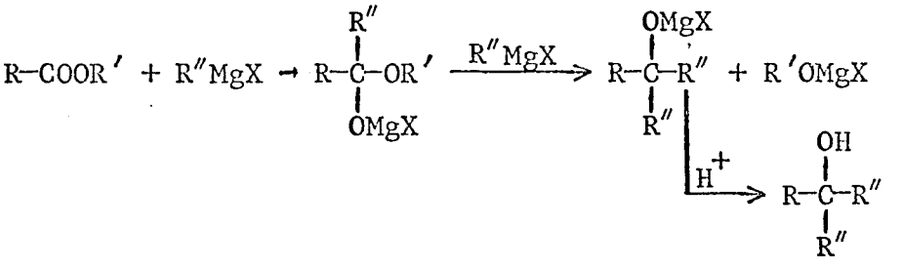
An infrared spectrum of the white solid product matched the spectrum of N-benzylbenzamide, but the melting point of the product was approximately 15° lower than the melting point of N-benzylbenzamide. Only after repeated recrystallizations using a wide range of solvents was the melting point of the product made to match that of N-benzylbenzamide. It is interesting to speculate that perhaps benzil or benzoin was produced in small yields by the above mechanism. A study of the infrared spectrum of the reaction products yielded no conclusive evidence concerning this possibility.

Grignard Reactions of Tribenzamide

Investigation of the action of Grignard reagents on tribenzamide leads to the conclusion that tertiary amides react similarly to esters, amides, and acid anhydrides. The reactions followed a pattern, and the products obtained appeared to be dependent on the type of Grignard reagent used.

An ester-type reaction was observed when phenylmagnesium bromide was used as the Grignard reagent. The main product was triphenylcarbinol. However, when aliphatic Grignard reagents were used, ketones were always produced. With methylmagnesium bromide, acetophenone was produced; ethylmagnesium bromide yielded propiophenone; with hexylmagnesium bromide, hexyl phenyl ketone was obtained. Even when an eight-fold excess of Grignard reagent was used, these ketones were isolated.

The simplest explanation of these results is that with aromatic Grignard reagents, tertiary amides react as esters do in the manner described by Grignard[45], i.e.,



But with aliphatic reagents, tertiary amides react as primary amides do in the manner described by Maxim[39] to yield only ketones.

In the reaction between tribenzamide and phenylmagnesium bromide, it is clear that benzophenone is formed before hydrolysis, and this ketone is attacked by another mole of Grignard reagent to yield

triphenylcarbinol. However, in the reaction between tribenzamide and an aliphatic Grignard reagent, the ketone must be formed after hydrolysis:

(1) $C_6H_5-CO-N(CO-C_6H_5)_2 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2C(O-MgBr)-N(COC_6H_5)_2 \rightarrow$

$(C_6H_5)_2CO + BrMgN(COC_6H_5)_2$

$\downarrow C_6H_5MgBr$

$(C_6H_5)_3C-OMgBr \xrightarrow{H^+} (C_6H_5)_3C-OH$

(2) $C_6H_5CO-N(CO-C_6H_5)_2 \xrightarrow{RCH_2MgBr} C_6H_5-C(O-MgBr)(CH_2-R)-N(COC_6H_5)_2 \xrightarrow{H^+}$

$C_6H_5COCH_2-R + BrMgN(COC_6H_5)_2$

An explanation for this phenomenon has been offered[27a]: The phenylmagnesium bromide reacts with tribenzamide to form the Grignard addition product which undergoes elimination to yield benzophenone because of a relative strain due to steric factors caused by the large phenyl groups which are attached to the carbonyl carbon. This steric strain is not nearly as great when aliphatic Grignard reagents are used; therefore, bond rearrangement is not as likely to occur.

The theory that steric factors play a large role in determining the final products in reactions between tertiary amides and Grignard reagents is supported by the work of Bell.[12] He obtained only acetophenone from the reaction of triacetamide and phenylmagnesium bromide.

Tissier and Grignard[42] reported that tertiary alcohols were produced when ethereal solutions of acetic or benzoic anhydride were added to ethereal methylmagnesium iodide. Fournier[57] showed that in reactions employing high dilution and reverse addition, and operating at Dry Ice temperature, the first step is ketone and acid formation.

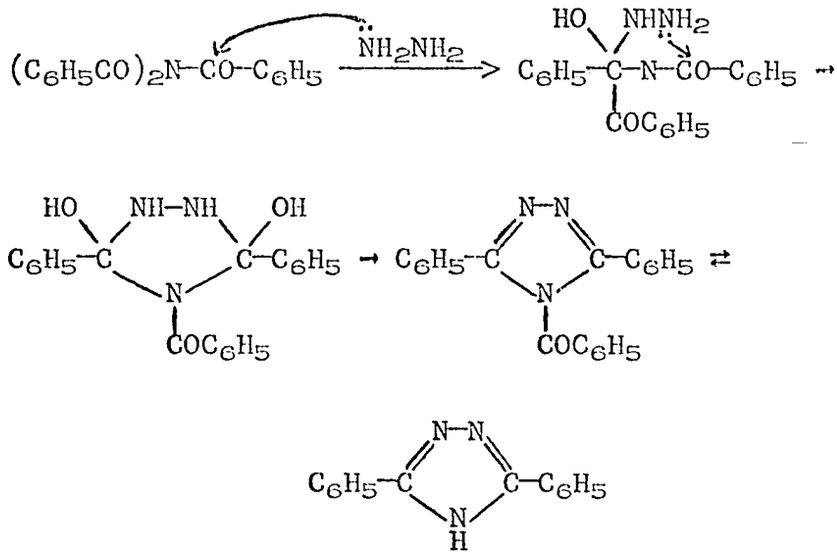
Newman[58] showed that ketones could be stabilized at temperatures of approximately -70°C, and that their solubilities were decreased. By using temperatures ranging from 34°C to -37°C, Newman and Smith[43] were able to obtain 2-hexanone in 51% yield by the reaction of acetic anhydride and n-butylmagnesium bromide. This yield of hexanone was increased to 83% by lowering the temperature to -80°C. These observations support the results obtained when tribenzamide was reacted with alkyl Grignard reagents, i.e., that ketones can be produced and can survive in an environment which would ordinarily be conducive to further attack of the ketone by a Grignard reagent. However, at the relatively high temperatures employed in this investigation, it is much more likely that ketones and Grignard reagents do not coexist, and that the ketone is formed only when the reaction mixture is hydrolyzed.

An attempt was made to react t-butylmagnesium bromide with tribenzamide. The product obtained was a brown, extremely viscous oil which could not be distilled or recrystallized.

Reaction of Tribenzamide and Amines

Prior investigations in this laboratory[27a,b] have shown that when hydrazine hydrate was added to tertiary amides which were partially dissolved in hot ethanol, the symmetrical diaroylhydrazines were produced.

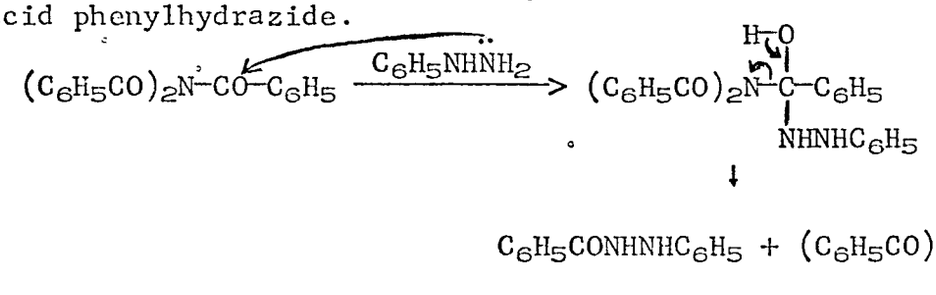
It was at first speculated that the reaction between tertiary amides and hydrazine might proceed in a manner analogous to the reaction of secondary amides with hydrazine to yield 3,5-disubstituted-1,2,4 triazoles.[37] Triazole formation might proceed as follows:



It is not surprising that the above reaction did not occur since, as was pointed out earlier, tertiary amides cannot assume the syn planar conformation; therefore, their carbonyl groups are not positioned so as to favor formation of the five-membered triazole ring.

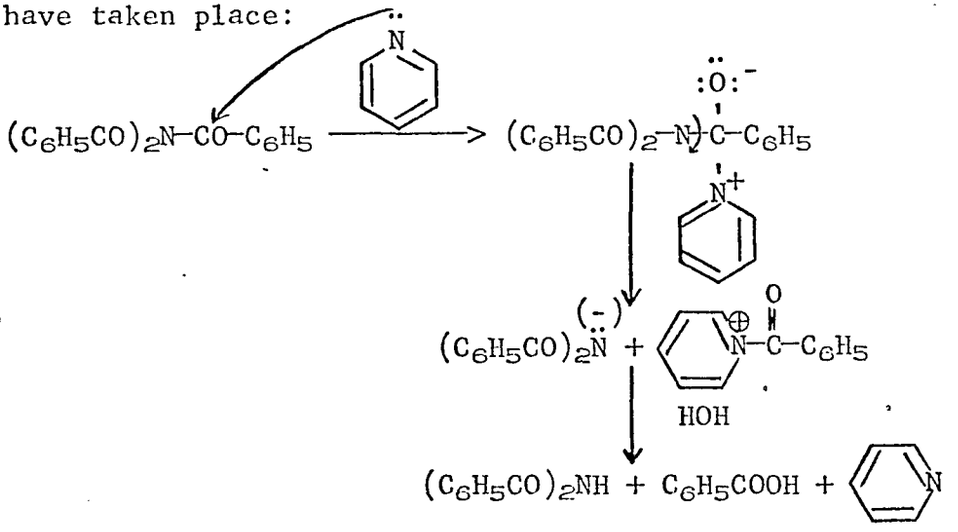
Hydrazinolysis is also favored by the fact that tertiary amides are more reactive toward nucleophilic displacement than are secondary amides.

When tribenzamide was reacted with phenylhydrazine, the expected nucleophilic attack occurred on the carbonyl carbon. Whereas in the hydrazine reaction, the tertiary amide was again attacked by the N-benzoylhydrazine to yield the diaroylhydrazine, in the phenylhydrazine reaction, further attack on the tertiary amide molecule was not possible due to steric hindrance. The end product in this reaction was benzoic acid phenylhydrazide.

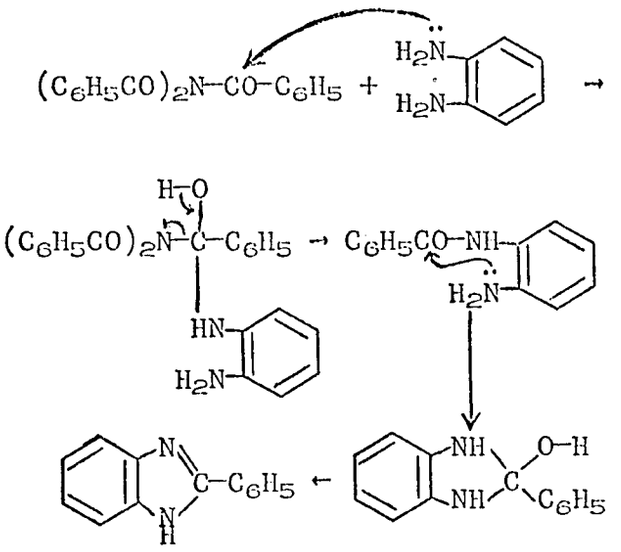


Amines which did not present steric problems reacted readily with tribenzamide to yield N-substituted benzamides. This reaction was observed when benzylamine and ethylamine were the nucleophilic agents employed. Diethylamine did not react with tribenzamide in a satisfactory manner. Extremely small yields of dibenzamide were obtained as well as small quantities of a crystalline material which possessed a wide melting range (180°-186°C) and which could not be purified. Dibenzylamine did not react with tribenzamide, probably because of steric hindrance.

When tribenzamide was refluxed in pyridine, a nucleophilic attack on the carbonyl carbon obviously took place. The products isolated were dibenzamide (40%) and benzoic acid (75%). The following reaction must have taken place:

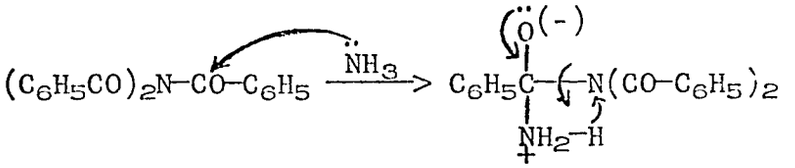


An interesting reaction was observed when tribenzamide was reacted with o-phenylenediamine. A white crystalline compound was obtained which possessed a melting point of 290°-293.5°C. The compound was identified as 2-phenylbenzimidazole by a comparison of its infrared spectrum with the spectrum of 2-phenylbenzimidazole. The mechanism for the reaction is as follows:



The driving force for this reaction is formation of the more extensive aromatic system.

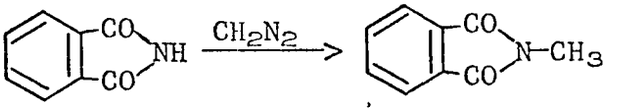
Ammonia was also caused to react with tertiary amides and gave the expected products, the primary and the secondary amides.



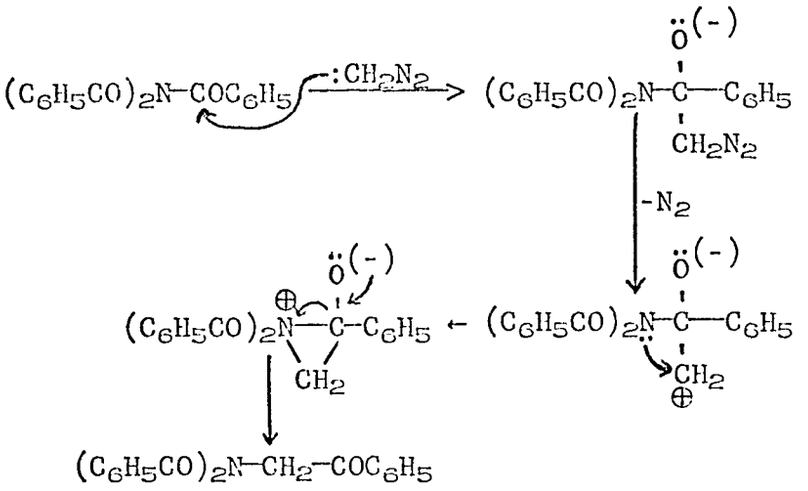
$$\rightarrow C_6H_5CONH_2 + (C_6H_5CO)_2NH$$

Reaction with Diazomethane

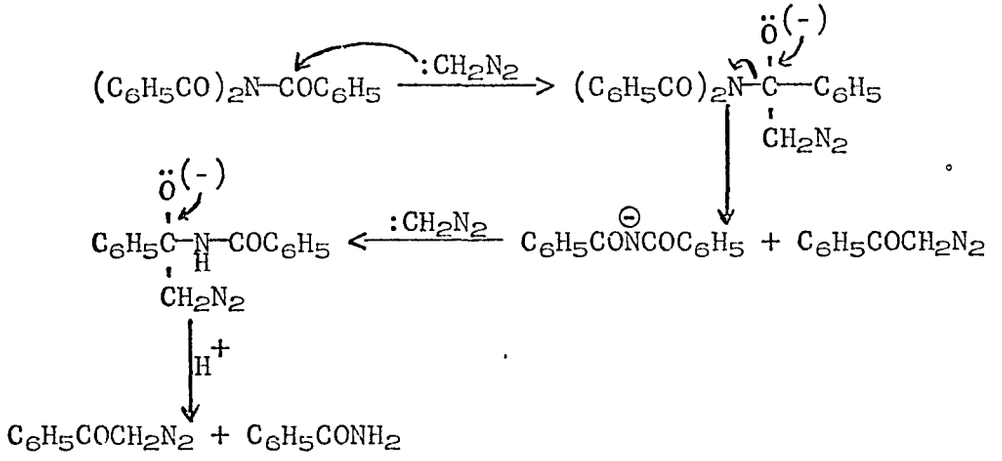
Earlier investigators[49,50] studied the reaction of diazomethane with various imides and obtained N-methylated products, e.g.,



Since it is impossible for tertiary amides to undergo a similar reaction, it was anticipated that the nucleophile, diazomethane, might attack the carbonyl carbon of the tertiary amides. If this attack did occur, the following rearrangement might be expected:



The above reaction was not observed, but it is possible that the initial attack on the carbonyl carbon did occur, with subsequent cleavage of the dibenzamide anion. Further attack by diazomethane on the dibenzamide carbonyl carbon could occur, cleaving off benzamide. Indeed, benzamide was the only product obtained from the reaction.



It might be argued that the dibenzamide, which was formed after the initial attack by the diazomethane on tribenzamide, would not undergo subsequent nucleophilic attack by the diazomethane on the carbonyl carbon, but would undergo N-methylation as did the imides mentioned earlier.[49,50] This objection can be answered by the explanation that the dibenzamide which is cleaved from the tribenzamide molecule is in the anionic form, and the negative charge on the nitrogen atom prevents

further attack by the diazomethane at this site. The only other place for attack to occur is at the carbonyl carbon.

Another question might be raised as to the fate of the benzoyldiazomethane which would be produced by the above mechanism. The reaction was run in methanol solvent. It is possible that the methanol reacted with the benzoyldiazomethane to yield α-methoxyacetophenone.

$$C_6H_5COCH_2N_2 \xrightarrow{CH_3OH} C_6H_5COCH_2OCH_3$$

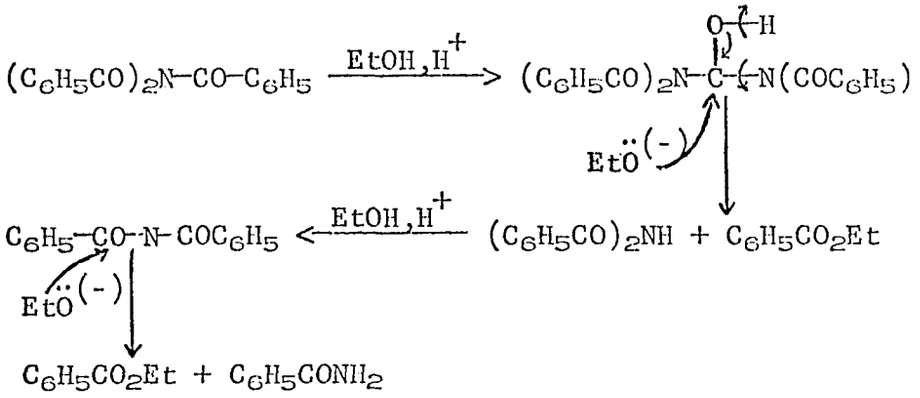
Although this product was not isolated, a more careful work-up of the products could possibly reveal its presence.

It was shown that benzamide was not produced simply as a result of attack on the tribenzamide by methanol. A control reaction was run employing the same conditions and the same reactants (with the exception of diazomethane) and tribenzamide was recovered unreacted.

Alcoholysis of Tribenzamide

Cowart[27b] had previously reported that the alcoholysis of 4,4',4''-trichlorotribenzamide gave the expected ester and the primary amide contaminated with small amounts of the secondary amide.

Similar results were obtained when tribenzamide was reacted with ethanol, using sulfuric acid as a catalyst. The suggested mechanism consists of a straight-forward nucleophilic attack by the ethoxide ion on a carbonyl carbon, followed by cleavage and formation of the ester and secondary amide. Apparently, a subsequent attack by an ethoxide group on one of the secondary amide carbonyls takes place, and more ester is formed.



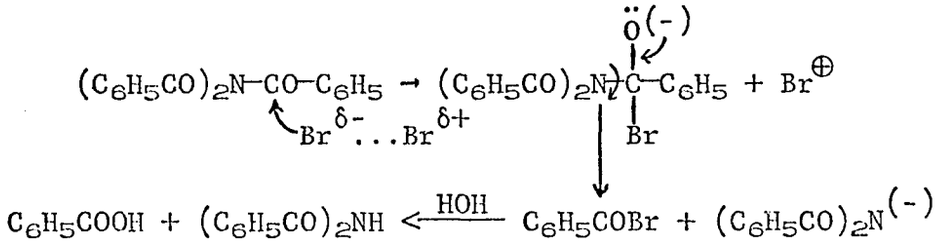
Reaction of Tribenzamide with Bromine

Electrophilic attack of Br_2 on the phenyl ring was not expected, and, indeed did not occur. Bromine reacted with tribenzamide in a manner similar to the reaction described by Tyka[24] in which bromine was made to react with tribenzoylphosphine to yield benzoyl bromide and phosphorus tribromide.

$$(C_6H_5CO)_3P + 3Br_2 \rightarrow 3C_6H_5COBr + PBr_3$$

With tribenzamide as the substrate, the reaction with bromine did not proceed as far as did the above reaction. Instead, cleavage occurred after the initial attack by bromine, and the end products were benzoic acid and dibenzamide.

Presumably, one of the tribenzamide carbonyl carbons was attacked by the relatively negative portion of the polarized bromine molecule. Cleavage of the molecule followed producing dibenzamide and benzoyl bromide, which was hydrolyzed to benzoic acid.



Reaction with Sulfuric Acid

It was anticipated that tribenzamide might be protonated by sulfuric acid to form the ammonium salt. However, the high susceptibility of the carbonyl carbon of tertiary amides to nucleophilic attack was once again demonstrated when simple protonation did not occur; instead, the sulfate anion attacked the carbonyl carbon to produce benzoic acid. The reaction thus was similar to the reaction between tribenzoylphosphine and sulfuric acid.[24]

$$(C_6H_5CO)_3P + H_2SO_4 \rightarrow PH_3 + 3C_6H_5COOSO_3H \xrightarrow{H_2O} 3C_6H_5COOH + 3H_2SO_4$$

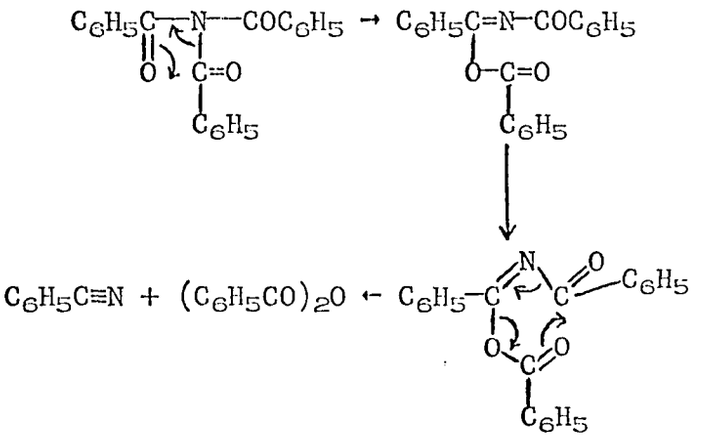
Pyrolysis of Tribenzamide

Curtius[3] had reported that tribenzamide sublimed undecomposed. LaCarna[59] recently pyrolyzed tricinnamamide and obtained cinnamamide and another solid product which was not identified. It was then speculated that tribenzamide might also be decomposed upon pyrolysis and that the report made by Curtius[3] was in error.

When tribenzamide was heated in a flask to a high temperature, it melted, vaporized, and condensed. The products which were obtained were benzonitrile and a high-melting, white, crystalline compound which was not identified. When tribenzamide was pyrolyzed in a sealed evacuated tube, benzonitrile was again produced, but the high-melting solid was not obtained; the material which remained was a dark brown char.

It is interesting to note that Wichelhaus[4] reported the preparation of triacetamide by the reaction of acetic anhydride with acetonitrile. As was stated earlier, however, his product is believed to have been the isomeric imidoester structure as shown on page 3.

It is suggested that the initial product formed in pyrolysis is the imidoester, and that this compound, upon further heating, yields benzonitrile and benzoic anhydride. These transformations are as follows:



Reaction of Tribenzamide with Acid Chlorides

It was thought that tertiary amides might be made to undergo acyl or aroyl group exchange with acid chlorides, e.g.,

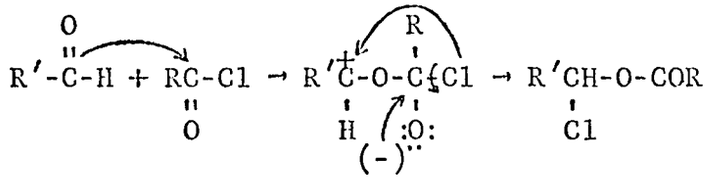
$$(C_6H_5CO)_3N + CH_3COCl \rightarrow (CH_3CO)_3N + C_6H_5COCl$$

This reaction was not observed, however - the only products obtained were the diamide and the corresponding acid.

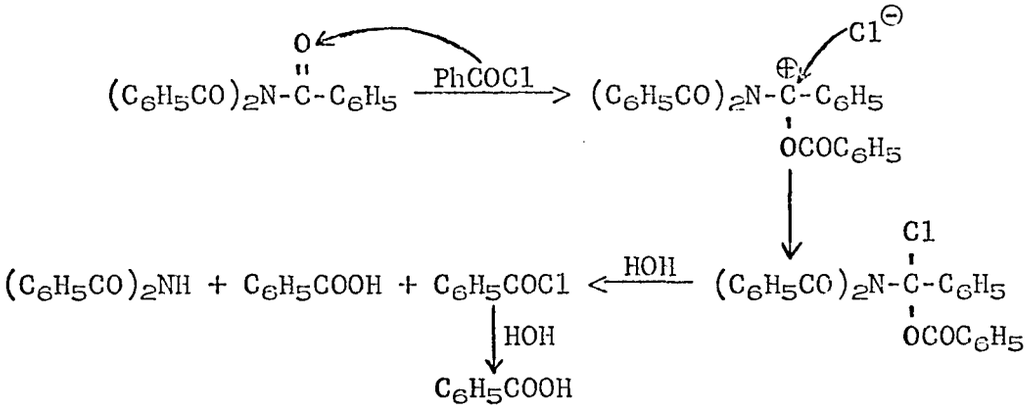
If it is assumed that moisture was present in the reaction flask, the acid chloride would then be hydrolyzed to the organic acid and to hydrochloric acid, which would then attack the tertiary amides and the above products could be explained. Since all precautions were taken to exclude moisture from the reaction, it is possible that the reaction proceeded in a manner similar to the reaction between acid chlorides and aldehydes performed by Adams and Vollweiller.[60]

$$RCOCl + R'CHO \rightarrow R'\text{-}\underset{\displaystyle Cl}{\underset{|}{CH}}\text{-}O\text{-}COR$$

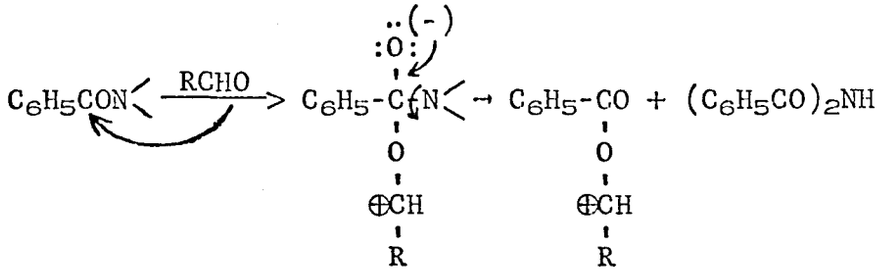
While no mention is made of the reaction mechanism, the reaction probably proceeds as follows:



If tribenzamide is placed in the role of the aldehyde, the products, dibenzamide and benzoic acid, might be explained by the following mechanism:



If tribenzamide is envisioned as the acid chloride in the reaction between aldehydes and acid chlorides, we might expect the following reaction to occur:



However, attempted reaction with aldehydes did not produce satisfactory results. Tribenzamide was obtained unreacted.

Attempted Friedel and Crafts Reaction with Tribenzamide

As was stated earlier, tertiary amides might serve as excellent acylating agents because loss of an acyl or aroyl group would relieve

steric interference around the nitrogen atom in the tertiary amide molecule. Kocheshkov[11] stated that triacetamide easily acylates a number of representative compounds and that any one of the three acyl groups would participate in acetylation reactions. He also stated that tertiary amides would undergo transacylation reactions.

Tyka[24] has reported the use of tertiary amides in Friedel-Crafts acylation and aroylation of benzene. He has reported that the reaction of tribenzamide with benzene under Friedel-Crafts reaction conditions yields benzophenone. He also obtained benzophenone by the reaction of tribenzoylphosphine and benzene using aluminum chloride as the catalyst. The following mechanism was proposed:

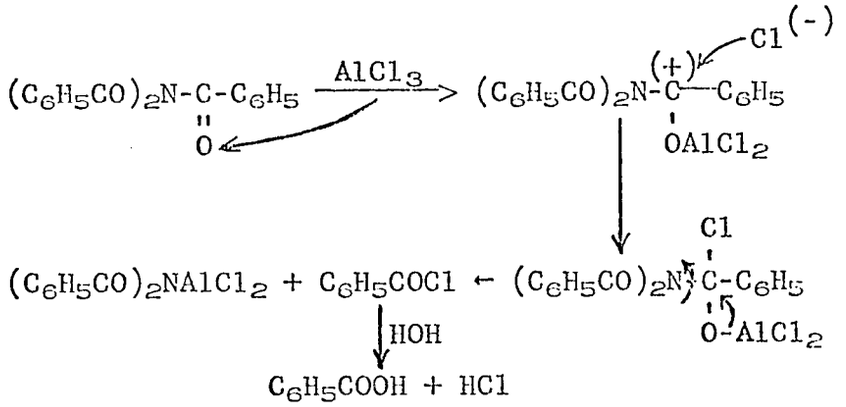
$$(C_6H_5CO)_3P + AlCl_3 \rightarrow [(C_6H_5CO)_3P \rightarrow AlCl_3] \rightarrow$$

$$C_6H_5CO^{(+)} + [(C_6H_5CO)_2P \rightarrow AlCl_3]^{(-)}$$

$$\xrightarrow{C_6H_6} (C_6H_5)_2CO \qquad \xrightarrow{H^+} [(C_6H_5CO)_2PH \rightarrow AlCl_3]$$

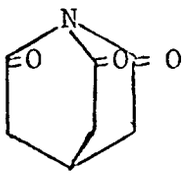
No success was achieved in this laboratory when an attempt was made to benzoylate benzene using tribenzamide as the aroylating agent. Since subtle differences may have existed in the experimental methods used in the present investigation as compared to the methods used by Tyka, the statement cannot be made that Tyka's observations were in error.

The reaction of tribenzamide, benzene, and aluminum chloride yielded only benzoic acid. This product might arise from attack on the tribenzamide by hydrochloric acid which could have been produced if moisture were present in considerable quantity in the reaction flask, thus hydrolyzing the aluminum chloride. However, since moisture was excluded, benzoic acid could be produced by the following mechanism:



Attempts to Synthesize Compounds Related to Tertiary Amides

The synthesis of a bycyclic tertiary amide such as that shown



would be of extreme interest for a number of reasons. It is clear that such a structure would force the nitrogen to assume a pyramidal structure and would prevent the lone pair of electrons on the nitrogen from participating in resonance. If, as is argued, tertiary amides in general are indeed pyramidal, the bicyclic compound should be entirely feasible. Molecular models of the compound show that there is some strain involved, although this strain does not appear to be of the magnitude necessary to prevent the existence of the bicyclic compound. Certainly there is as much internal strain in other organic compounds which have been synthesized.

It was anticipated that the bicyclic tertiary amide might be synthesized by the following route:

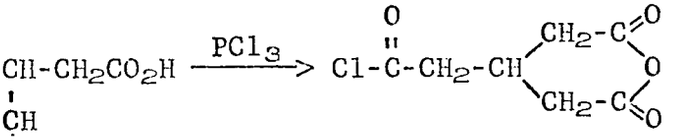
(1) $CH_3O_2CCH_2\text{-}CO\text{-}CH_2CO_2CH_3 \xrightarrow{NaBH_4} CH_3O_2CCH_2\text{-}CH(OH)\text{-}CH_2CO_2CH_3$

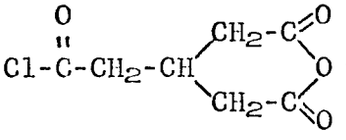
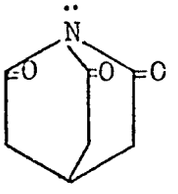
(2) $CH_3O_2CCH_2\text{-}CH(OH)\text{-}CH_2CO_2CH_3 \xrightarrow[C_6H_6]{(CH_3CO)_2O} CH_3O_2CCH_2\text{-}CH{=}CHCO_2CH_3$

(3) $CH_3O_2CCH_2\text{-}CH{=}CHCO_2CH_3 \xrightarrow[\text{via Michael}]{(-)_{CH(CO_2Et)_2}} CH_3O_2CCH_2\text{-}CH(CH(CO_2Et)_2)\text{-}CHCO_2CH_3$

(4) $CH_3O_2CCH_2\text{-}CH(CH(CO_2Et)_2)\text{-}CH_2CO_2CH_3 \xrightarrow{H^+} HO_2CCH_2\text{-}CH(CH(CO_2H)_2)\text{-}CH_2CO_2CH_3$

(5) $HO_2CCH_2\text{-}CH(CH(CO_2H)_2)\text{-}CH_2CO_2H \xrightarrow{-CO_2} HO_2CCH_2\text{-}CH(CH)(CO_2H)\text{-}CH_2CO_2H$

(6) $HO_2CCH_2\text{-}CH(CH)(CO_2H)\text{-}CH_2CO_2H \xrightarrow{PCl_3}$ 

(7)  $\xrightarrow{NH_3}$ 

The synthesis proceeded only as far as the dehydration step (2). The Michael addition could not be achieved.

An alternate synthetic route was attempted without success.

(1) $CH_3O_2CCH_2COCH_2CO_2CH_3 \xrightarrow{BrZnCH_2CO_2Et} CH_3O_2CCH_2\text{-}C(OH)(CHCO_2Et)\text{-}CH_2CO_2CH_3$

(2) $CH_3O_2CCH_2\text{-}C(OH)(CHCO_2Et)\text{-}CH_2CO_2CH_3 \xrightarrow{-H_2O} CH_3O_2CCH_2\text{-}C(CHCO_2Et){=}CHCO_2CH_3$

(3) $CH_3O_2CCH_2\text{-}C(CHCO_2Et){=}CHCO_2CH_3 \xrightarrow{H_2/Pd} CH_3O_2CCH_2\text{-}CH(CHCO_2Et)\text{-}CH_2CO_2CH_3$

The remainder of the synthesis is similar to the above. In this attempt, the Reformatsky reaction failed. There is no apparent reason why the Reformatsky reagent should not react with the keto ester starting compound, although no references to such a reaction could be found in the literature.

An attempt was made to synthesize the arsenic and antimony analogs of tribenzamide without success. Tyka[24] had reported the preparation of $(C_6H_5CO)_3P$ by the reaction of phosphine with benzoyl chloride in pyridine solution. It would appear that the larger sizes of the antimony and arsenic atoms would be conducive to the placement of three aroyl groups around them.

The best explanation for the success in preparing tribenzoylphosphine, and the failure in preparing the arsenic and antimony analogs, is that phosphorus, like nitrogen, is essentially covalent in all of its chemistry, whereas arsenic and antimony show increasing metallic behavior.[61] Therefore, arsenic and antimony would be more apt to form ionic compounds instead of covalent compounds. The bonding in triaroylphosphines, of course, is of a covalent nature.

EXPERIMENTAL PART

Preparation of Tribenzamide (1)

The starting material, tribenzamide, was prepared by the method of Thompson.[7]

A solution of 7.03 g (0.05 mole) of benzoyl chloride in 55 ml of chloroform was cooled to -60°C. Pyridine (5 ml) was added, and then 3.03 g (0.025 mole) of pure, finely-powdered benzamide was added. The reaction mixture was maintained at -60°C for 20 hr, with constant stirring. At the end of the reaction time, 5 ml of ethanol was added, and the reaction mixture was allowed to come to room temperature.

The chloroform solution was washed with two 60 ml portions of cold 1 N hydrochloric acid and once each with similar volumes of 0.5 N sodium hydroxide and distilled water. The chloroform was evaporated over a steam cone, and the remaining oil was cooled and allowed to crystallize. The tribenzamide, obtained in approximately 85% yield, was recrystallized from acetone and water. The melting point was 208°-210°C.

Preparation of Tribenzamide (2)

This method of preparation was analogous to the method used by Tyka[24] in his preparation of tribenzoylphosphine.

A solution of benzoyl chloride (25%) in dry pyridine was prepared, and anhydrous ammonia was slowly bubbled into this solution at room temperature for about ten minutes. A white product immediately precipitated. It was speculated that this product was a mixture of dibenzamide and tribenzamide. It was recrystallized by heating in acetone

until the solution was clear, then adding water until the solution was turbid, and then heated again to boiling. The hot solution was gravity-filtered and cooled, and the precipitated product vacuum-filtered. The melting point was 206°-208°C, and the yield was 20%.

Reaction of Tribenzamide and t-Butylmagnesium Bromide

t-Butylmagnesium bromide was prepared in ether by ordinary methods.[62] Theoretically, the reaction produced 0.083 mole of Grignard reagent. Tribenzamide (3.3 g, 0.01 mole) was added little by little to the flask containing the t-butylmagnesium bromide. This mixture was then hydrolyzed by carefully pouring it into a 250 ml beaker containing 40 g ice and 15 ml of concentrated hydrochloric acid.

The ether layer was separated from the aqueous layer and washed with 50 ml water, 50 ml of 1% sodium bicarbonate, and again with 50 ml of water. Upon removal of the ether by use of a steam cone, a brown, highly viscous oil remained. All efforts to obtain a purified product failed. The infrared spectrum indicated the presence of a carbonyl group and a hydroxyl group.

Lithium Aluminum Hydride Reduction: A 600 ml round-bottom three-necked flask was fitted with a Friedrich ice-water condenser, a dropping funnel, and a stirrer. Sodium-dried tetrahydrofuran (200 ml) was placed in the flask, and a small amount of lithium aluminum hydride was added to react with any moisture present. After effervescence ceased, 1.14 g (0.03 mole) of lithium aluminum hydride was placed in the tetrahydrofuran.

Tribenzamide (3.3 g, 0.01 mole) was dissolved in 200 ml of dried tetrahydrofuran. This solution was added dropwise to the lithium

aluminum hydride solution, and the resulting mixture was refluxed gently with stirring for four hours. The solution developed a cherry-red color shortly after the reaction had started.

Ethyl acetate was carefully added at the end of the reaction in order to destroy excess lithium aluminum hydride. Sulfuric acid (2 N) was then added in order to hydrolyze the product. The organic layer was separated from the water layer and dried with calcium chloride.

The tetrahydrofuran was evaporated on a steam cone with the help of a stream of air. White crystals came out of solution. The product was recrystallized from acetone and water, and the crystals were recovered by vacuum filtration. The product, which melted at 102°-103°, was identified as N-benzylbenzamide by a comparison of its infrared spectrum with that of a known sample. The yield was 0.68 g (32%). The reaction was repeated several times using different concentrations, temperatures, solvents and reaction times with similar results.

Lithium Diethoxyaluminohydride Reduction: The experimental procedure used in this reaction was essentially the same as the one used by Brown and Tsukamoto[8] in their reduction of N,N-dimethylamides to aldehydes.

A 1000 ml round-bottom three-necked flask was fitted with an ice-water condenser, a stirrer, and a dropping funnel. A solution of 8.8 g (0.234 mole) of lithium aluminum hydride in 200 ml of anhydrous ether was prepared in the flask, and the mixture was cooled to 0°C in an ice-water bath. A solution of 20.6 g (0.234 mole) of ethyl acetate in 150 ml of anhydrous ether was added dropwise to the lithium aluminum hydride solution in order to form the lithium diethoxyaluminohydride.

After all the ethyl acetate had been added, 9.9 g (0.03 mole) of tribenzamide was added in small portions to the stirred mixture. The reaction was allowed to proceed at 0°C for 30 min.; then the mixture was refluxed gently for 30 min. At the end of the reaction time the mixture was again cooled to 0°C and hydrolyzed by adding dropwise 100 ml of 2 N sulfuric acid.

The ether layer was separated from the aqueous phase; the aqueous layer was washed twice with 50 ml portions of ether, and the extracts were added to the ether layer. The ether layer was dried over calcium chloride and then filtered through a fluted filter into an Erlenmeyer flask. The ether was removed by use of a steam cone and a jet of air. Benzaldehyde was separated from the product mixture by addition of 2,4-dinitrophenylhydrazine in ethanol. After removal of the benzaldehyde 2,4-dinitrophenylhydrazone, N-benzylbenzamide separated from the filtrate; the yield was 1.9 g (90%). The product was identified by its melting point (103°) and by a comparison of its infrared spectrum with that of a known sample.

Zinc and Acetic Acid Reduction: Zinc dust (6.5 g, 0.1 mole) was placed in a 125 ml round-bottom flask to which was added 50 ml of glacial acetic acid and 2 ml of water. Tribenzamide (3.3 g, 0.01 mole) was then placed in the flask, which was then fitted with an ice-water condenser. This mixture was refluxed for 72 hours. After the reaction time, any solid was removed by gravity-filtration, and the filtrate was neutralized with 1 N sodium hydroxide. The product was extracted with ether and the ether was removed by use of a steam cone.

The white solid product obtained was recrystallized from benzene and was identified as N-benzylbenzamide by its melting point (102°-103°C) and its infrared spectrum. The yield was 1.65 g (84%).

Diborane Reduction: In a 300 ml one-neck round-bottom flask was placed a solution of 3.3 g (0.01 mole) of tribenzamide and 1.89 g (0.05 mole) of sodium borohydride dissolved in 100 ml of dry diglyme. While this mixture was being stirred with a magnetic stirrer, 4.3 g (0.03 mole) of boron trifluoride etherate dissolved in 10 ml of diglyme was dropped in, and the mixture was stirred for a further two hours.

The reaction mixture was hydrolyzed by pouring it over a mixture of crushed ice and hydrochloric acid, and the resulting precipitated white solid was filtered by suction. It was recrystallized from 95% ethanol, and its melting point was found to be 102°-103°. Its infrared spectrum was identical to that of N-benzylbenzamide. An infrared spectrum of the filtrate from the vacuum filtration indicated the presence of benzyl alcohol.

Sodium Borohydride Reduction: Tribenzamide, 3.3 g, was dissolved in 80 ml of tetrahydrofuran in a 125 ml Erlenmeyer flask. This solution was added slowly to a solution of 0.5 g of sodium borohydride and 0.1 g of sodium hydroxide in 50 ml H_2O, stirring being maintained throughout the addition by use of a magnetic stirrer. The reaction mixture was stirred for a period of 48 hours, after which time 10 ml of 2 N sulfuric acid was added and the product was extracted with chloroform. A white crystalling product was obtained and was recrystallized from acetone and water. It was identified as N-benzylbenzamide by its melting point and infrared spectrum. The yield was 0.85 g (43%).

Other Attempts to Reduce Tribenzamide:

Sodium in alcohol - Tribenzamide (3.3 g) in 200 ml of ethanol was added all at once to 2 g of sodium metal in 100 ml of toluene. This mixture was placed on a steam cone in order to remove the ethanol and toluene.

White crystals came out of solution. These were recrystallized from benzene and collected by vacuum filtration. The melting point was 125°-126°C, and the infrared spectrum matched the spectrum of benzamide. The yield was 0.8 g (66%). An infrared spectrum of the distilled filtrate matched the spectrum of ethyl benzoate.

Catalytic hydrogenation - Tribenzamide (3.3 g) was dissolved in 200 ml of tetrahydrofuran. One gram of palladium-carbon catalyst was added and the mixture was placed in a Paar low pressure hydrogenator under 30-40 pounds pressure of hydrogen for a period of 24 hours. Shaking was maintained throughout the reaction.

The catalyst was removed by gravity filtration. The tetrahydrofuran was evaporated, but only unreacted tribenzamide was recovered. No reduction product was obtained.

Clemmensen reduction - Zinc metal (4 g), 0.4 g of mercurous chloride, 1 ml of concentrated hydrochloric acid, and 3 g of tribenzamide dissolved in 150 ml of tetrahydrofuran were placed in a 300 ml round-bottom flask. The flask was fitted with a reflux condenser, and the mixture was refluxed for two to three hours. It was then allowed to stand overnight. The mixture was washed with two 150 ml portions of anhydrous ether, aqueous sodium hydroxide was added to the aqueous phase, and the ether layer which appeared was separated. The combined ether was removed by distillation. No reduction product was obtained.

Alcoholysis of Tribenzamide

In a 500 ml one-neck round-bottom flask was placed 3.3 g (0.01 mole) of tribenzamide, 250 ml of absolute ethanol, and one drop of concentrated sulfuric acid. A condenser was attached and the mixture refluxed for 24 hours. The ethanol was removed by distillation; a white solid precipitated and was separated by vacuum filtration.

The filtrate was distilled, and 0.93 g (31%) of ethyl benzoate was recovered at 211°-213°C. The solid was recrystallized from hot water and was found to possess a melting point of 126°-127°C. It was identified as benzamide by its infrared spectrum. The yield was 0.74 g (61%).

Reaction with Diazomethane

Potassium hydroxide (5 g) was dissolved in 10 ml water in a 125 ml Erlenmeyer flask; 50 ml of ether was added and the mixture cooled to 0°C in an ice bath. In a separate 125 ml Erlenmeyer flask tribenzamide (3.3g), was placed in a mixture of 20 ml methanol and 50 ml chloroform and cooled to 0°C. Nitrosomethylurea (1.03 g, 0.04 mole) was dissolved very carefully in the potassium hydroxide solution; the mixture was stirred for 15 minutes on a magnetic stirrer after the last addition of nitrosomethylurea. This solution was then placed in a separatory funnel and the water layer removed; glacial acetic acid was added to the water to destroy any diazomethane present.

The ether solution of diazomethane was added drop by drop to the stirred tribenzamide solution. After all of the ether solution had been added, the reaction flask was stoppered and left on the magnetic stirrer overnight.

At the end of the reaction time, 10 drops of glacial acetic acid was added to the reaction mixture to destroy excess diazomethane. The flask was placed under a stream of air in order to evaporate the ether and methanol. A cloudy solution remained after evaporation was complete.

A vacuum distillation was attempted, but upon applying the vacuum, the material in the distilling flask turned milky, so the distillation was discontinued. Petroleum ether was added to the cloudy solution in an effort to extract any impurities which might prevent crystallization. Shaking the petroleum ether solution led to the appearance of a white precipitate. The product was separated by vacuum-filtration and found to possess a melting point of 125°-127°. It was identified as benzamide by its infrared spectrum.

Reaction of Tribenzamide and Sulfuric Acid

(1) In a 100 ml Erlenmeyer flask were placed 1.7 g (0.005 mole) tribenzamide and 10 ml of concentrated sulfuric acid. This mixture was heated to 150°C for a period of five minutes. The mixture was removed from the heat and 2 ml of water were added dropwise and the flask allowed to cool. The flask was filled with cold water and a white precipitate appeared. The product was vacuum-filtered and was identified as benzoic acid by a comparison of its infrared spectrum with that of benzoic acid. The yield was 1.1 g (90%).

(2) Tribenzamide (1 g) in 4 ml concentrated sulfuric acid was placed in a 25 ml Erlenmeyer flask and allowed to stand several days. The contents of the flask were then subjected to a stream of air and a white solid appeared. Water was added to the flask and the solid was vacuum-filtered. The product was recrystallized from ethanol and water and was found to be benzoic acid. The yield was 0.92 g (75%).

Bromination of Tribenzamide

In a 100 ml round-bottom flask fitted with an ice-water condenser were placed 1.7 g tribenzamide, 25 ml chloroform, and 0.5 g of iron filings. This mixture was heated until all the tribenzamide had dissolved. After refluxing had ceased, the condenser was removed so that bromine in excess could be introduced into the reaction flask. The condenser was again fitted in the flask and a delivery tube was attached to the condenser and extended into a sodium hydroxide trap.

The mixture was heated very gently for a period of one hour after which time the flask was placed under the vacuum hood and heated to drive off excess bromine.

The chloroform solution was gravity-filtered in order to remove the iron filings, and then the chloroform was evaporated. The white product which was obtained by vacuum filtration was identified as benzoic acid and was obtained in 60% yield. Another product was obtained in small amounts and its infrared spectrum matched that of dibenzamide.

Pyrolysis of Tribenzamide

(1) In a 50 ml round-bottom flask fitted with a Friedrich ice-water condenser was placed 1 g of tribenzamide. The flask was heated with a burner until the tribenzamide melted and then began to vaporize. Heating was continued for about five minutes and then the flask was left standing overnight. A white solid appeared and was removed from the liquid portion by vacuum-filtration. The product melted at 235°-237°C. The filtrate was found to be benzonitrile by a comparison of its infrared spectrum with that of benzonitrile.

(2) Approximately 0.25 to 0.5 g of tribenzamide was placed in a tube which was sealed at one end. The open end of the tube was connected to a vacuum pump and while the tube was being evacuated, it was being sealed by use of a torch. The tribenzamide in the tube was pyrolyzed as before, and the tube was then opened and the products examined. Benzonitrile was again formed, but the high-melting solid was not obtained.

Friedel and Crafts Reaction

In a 150 ml round-bottom flask fitted with a reflux condenser were placed 1.7 g tribenzamide, 25 ml of thiophene-free benzene and 15 g aluminum chloride. A calcium chloride tube was attached to the top of the condenser and connected to a gas trap.

The mixture was heated under reflux for 30 minutes. At the end of the heating period, the mixture was cooled in an ice-water bath and 20 ml of water followed by 5 ml concentrated hydrochloric acid were slowly added to the reaction mixture.

The benzene layer was separated from the aqueous phase and the benzene was distilled off. The brown, gummy substance which appeared was dissolved in acetone and water was added to reprecipitate the product, which was recrystallized from ethanol. The product was found to be benzoic acid instead of the expected benzophenone.

Reaction of Methyl Iodide and Tribenzamide

Tribenzamide (1.7 g, 0.005 mole) was dissolved in chloroform and 2 ml of methyl iodide was added and the mixture refluxed for 3 hours. No precipitate was formed, and unreacted tribenzamide was recovered upon evaporation of the chloroform.

A variation was attempted using dimethylsulfoxide as the solvent. Again, no reaction was observed.

Essentially the same procedure was followed in attempting a reaction using tribenzamide and p-bromophenacyl bromide, but again no reaction was observed.

Reaction of Amines and Tribenzamide

Tribenzamide and benzylamine - In a 150 ml round-bottom flask was placed 3.3 g of tribenzamide. Enough chloroform was added so that the tribenzamide would dissolve. Benzylamine (1.07 g, 0.01 mole) was added and the mixture refluxed for eighteen hours.

At the end of the reaction time, the chloroform was removed by distillation and a white product remained. Recrystallization from ether yielded two products. One melted at 102° to 103°C, and was identified as N-benzylbenzamide by its infrared spectrum. The other melted at 147° to 148°C and was identified as dibenzamide.

The reaction was repeated using excess benzylamine; no dibenzamide was obtained, N-benzylbenzamide being the only product.

Reactions of tribenzamide and other amines - Essentially the same procedure as above was employed with all amines.

Ethylamine yielded dibenzamide and N-ethylbenzamide. Diethylamine yielded a product which could not be purified well. No reaction was observed when diphenylamine was refluxed with tribenzamide. Pyridine reacted with tribenzamide to yield dibenzamide and benzoic acid.

Reaction of tribenzamide and o-phenylenediamine - In a 150 ml round-bottom flask fitted with a reflux condenser were placed 1.7 g (0.005 mole) of tribenzamide and 25 ml chloroform.

o-Phenylenediamine (0.54 g, 0.005 mole) was dissolved in absolute ethanol and this solution was added to the tribenzamide solution. The mixture was refluxed overnight, and the solvent was then removed by distillation. A crystalline product was obtained and recrystallized from ethanol and water. The melting point was 292° to 293°, and the product was identified from its infrared spectrum as 2-phenylbenzimidazole. The yield was 0.75 g (77%).

Reaction of tribenzamide and phenylhydrazine - Tribenzamide, 1.7 g, (0.005 mole) was dissolved as completely as possible in 100-125 ml of hot absolute ethanol in a 250 ml Erlenmeyer flask. As this mixture was boiled on a hot plate, 1 ml of phenylhydrazine was added. The mixture was heated until almost all of the ethanol had evaporated. Cooling led to the formation of a white product.

The product was collected by vacuum filtration and recrystallized by dissolving in hot benzene, cooling, and adding a few drops of hexane.

The compound obtained melted at 168° to 169.5°C and was identified by its infrared spectrum as benzoic acid phenylhydrazide. The yield was 0.42 g (62%).

Ammonolysis of Tribenzamide

In a 500 ml three-neck round-bottom flask fitted with a Dry Ice condenser was placed 3.3 g of tribenzamide. Anhydrous ammonia was allowed to flow into the flask, evaporate and condense for a period of eight hours. The reaction mixture was then boiled with 20 ml of water for several minutes and filtered. The filtrate was concentrated by partial evaporation and cooled, and the solid which precipitated was removed by filtration. This product was identified as benzamide.

Another product obtained from this reaction was dibenzamide.

Reaction of Benzoyl Chloride with Tribenzamide

In a 125 ml Erlenmeyer flask were placed 3.3 g of tribenzamide and 50 ml of chloroform. This mixture was placed on a steam cone and heated until the tribenzamide had dissolved. Benzoyl chloride (1.41 g, 0.01 mole) was added to the flask which was then fitted with a calcium chloride drying tube and placed on a magnetic stirrer and stirred for a period of five days. After the reaction period the chloroform was distilled off and the white solid product was collected by suction filtration and washed with 2 portions of cold water. It was recrystallized from warm benzene and was identified as dibenzamide by its melting point (146° to 148°) and its infrared spectrum. Another product was obtained during the recrystallization procedure. This product was recrystallized from water and identified as benzoic acid. The yield of dibenzamide was 0.9 g (40%) and the yield of benzoic acid was 0.92 g (41%).

The same procedure was employed in attempting to react acetyl chloride with tribenzamide. No satisfactory results were obtained.

Attempted Reaction of Aldehydes with Tribenzamide

Tribenzamide (1.7 g, 0.005 mole) was dissolved in chloroform in a 100 ml round-bottom flask. The aldehyde was added in excess and two drops of concentrated sulfuric acid were placed in the flask. The flask was fitted with an ice-water condenser and the mixture refluxed 24 hours. After removal of the chloroform and excess aldehyde by distillation, unreacted tribenzamide was obtained.

Attempted Synthesis of a Bicyclic Tertiary Amide

Preparation of Acetone Dicarboxylic Acid[63]:

(1) In a 5 l round-bottom flask, fitted with a mechanical stirrer was placed 3000 g of fuming sulfuric acid (20% SO_3). The flask was cooled to -5°C by means of a water, ice, and hydrochloric acid bath. Stirring was begun and 700 g of finely powdered U.S.P. citric acid was gradually added. The temperature was not allowed to rise above 0°C until half the citric acid had been added, after which the temperature was not allowed to exceed 10°C until the reaction was complete. The addition required 3-4 hours and stirring was continued until all of the citric acid was dissolved.

The temperature of the reaction mixture was allowed to rise gradually until a vigorous evolution of gas began. The flask was cooled to prevent excessive frothing, but the evolution of gas wasn't stopped entirely. After the more vigorous foaming had ceased, the temperature of reaction mixture was raised to about 30°C and kept there until no more foaming occurred. (Stirring was stopped for a minute and a clear brown liquid giving off very few gas bubbles resulted.). This general procedure required 2 to 3 hours.

The reaction mixture was cooled to 0°C and 2400 g of finely cracked ice was added in small portions. The temperature of the mixture was not allowed to rise above 10°C until one-third of the ice had been added; at this time, the temperature was allowed to rise to 25° to 30°C. The addition required about 2 hours. The reaction mixture was again cooled to 0°C and filtered as rapidly as possible through a funnel fitted with a porous plate. The crystals were thoroughly

pressed and sucked as dry as possible. The product was light gray to white in color. The solid was transferred to a beaker and stirred with 200 to 250 ml of ethyl acetate. The thick paste that resulted was filtered with suction. The yield was 450 to 475 g (92% to 97%).

(2) An easier method of preparation was employed by Ingold and Nickolls[64].

Two kilograms of fuming sulfuric acid were added as rapidly as possible, with constant stirring, to one kilogram of finely powdered hydrated citric acid. A considerable amount of heat was evolved and large volumes of carbon monoxide are produced. After fifteen minutes the mixture was cooled in a freezing-mixture (ice-salt), and one kilogram of crushed ice was added with stirring. When cold, the pasty mixture was vacuum-filtered and sucked dry. The yield was about 450 g (80%).

Preparation of Ethyl Acetonedicarboxylate[65]:

(1) The crude acid obtained from 700 g of citric acid was treated with 700 g of absolute ethanol to which had been added at least 130 g to 150 g of dry hydrochloric acid. The mixture was placed in a flask fitted with a calcium chloride tube, and was then heated to 45°C. The mixture was kept in the water bath at 40°C (bath temperature) with shaking until all the acid had dissolved (15 to 20 minutes). The mixture was then cooled to room temperature in the bath and allowed to stand for twelve hours.

At the end of this time, the contents of the flask were poured into 1300-1400 ml of ice water. The ester layer separated and the water-ethanol layer was extracted twice with one-half its volume of

benzene (700 ml). The benzene extract was added to the original ester, which had been separated. The total solution was washed with 400 ml 10% sodium carbonate solution, once with dilute sulfuric acid, and twice with 400 ml portions of water. The benzene was removed by evaporation on a steam bath.

The ester was distilled under reduced pressure. A small low-boiling fraction came off initially, then the ester distilled at 131° to 136°/9 to 10 m.m. pressure, or 145° to 148°/17 m.m. pressure. The yield was 284g to 315 g (42% to 46% based on citric acid).

(2) The method employed by Ingold and Nickolls[64] is as follows: Absolute ethyl alcohol (500 g) was saturated with hydrochloric acid and was treated at 0°C with 300 g of dry acetonedicarboxylic acid. The suspension was shaken frequently to aid solution of the acid, and kept at room temperature for forty-eight hours, after which time water was added and the ester extracted with ether.

The product was vacuum-distilled as above and the yield was 240 g (60%).

Reduction of Acetonedicarboxylate

Reduction was accomplished using the method of Fieser.[66] Diethyl acetonedicarboxylate (202 g, 1 mole) was dissolved in 125 ml of 95% ethanol. Excess sodium borohydride was carefully added to the solution, stirring maintained throughout the addition. Addition of sodium borohydride was completed when addition of the reducing agent no longer caused frothing. The reaction mixture was stirred overnight by use of a magnetic stirrer. After the reaction period, 100 ml of water was added; the mixture was heated to boiling, and then filtered. An additional 10 ml of water was added to the filtrate.

The product was extracted with ether and the ether layer was washed with water. The ether was removed by evaporation and the product was dried with anhydrous magnesium sulfate. An infrared spectrum of the liquid product indicated an hydroxyl peak.

Dehydration of Reduced Ethyl Acetonedicarboxylate:

The hydroxyester prepared from the above reduction was dehydrated as follows:

Acetic anhydride (100 ml), benzene (100 ml), and the hydroxyesters were placed in a 500 ml round-bottom flask fitted with a Dean-Starke trap. The mixture was refluxed and the water-benzene azestrope distilled into the trap.

The liquid product which remained was vacuum-distilled at 135° to 140°/ 2 m.m. The infrared spectrum showed an absence of the hydroxyl peak.

Attempt to Perform Michael Condensation of Malonic Ester and the Unsaturated Dicarboxylate

Two attempts were made to perform this reaction using two different methods employed by Conner.[67]

(1) To equimolar quantities of the two reactants dissolved in absolute ethanol (50 ml/0.1 mole of addendum) was added piperidine (2.0 ml/0.1 mole addendum), and the solution was heated 72 hours on a steam bath. The reaction mixture was then cooled in ice, any solid removed by filtration, and recrystallized.

When no solid was formed, the mixture was diluted with water, extracted with ether, and dried over sodium sulfate. The ether was removed by evaporation, but no condensation product was obtained.

(2) A solution of sodium ethoxide was prepared by dissolving Na metal in the minimum amount of absolute ethanol. Diethylmalonate (three to six times the number of moles of Na) was added followed by a solution containing the unsaturated ester (in an amount equimolar to the addendum) and a minimum of 2 l. of dry ether or thiophene-free benzene per mole of ester.

The reaction mixture was stirred by use of a magnetic stirrer for at least 20 hours at room temperature. At the end of the reaction time, the mixture was acidified with glacial acetic acid. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed by distillation. No condensation product was obtained.

Attempted Reformatsky Reaction Ethyl Bromoacetate and Ethyl Acetonedicarboxylate[68]

The zinc metal employed in this reaction was cleaned by immersing the 30-mesh metal in hot concentrated sulfuric acid containing a few drops of concentrated nitric acid for a period of minutes. The acid was then diluted by pouring into a large volume of water. The zinc was washed with water, then acetone, and dried.

In a clean, dry 500 ml three-neck round-bottom flask fitted with a mechanical stirrer, a 250 ml separatory funnel, and a reflux condenser, the upper end of which was protected by a calcium chloride tube, was placed 40 g (0.62 mole) of zinc dust. A solution of 83.5 g (0.5 mole) of ethyl bromoacetate and 125 g (0.61 mole) of ethyl acetonedicarboxylate in 80 ml of dry benzene and 20 ml absolute ether was placed in the separatory funnel. Approximately 15 ml of this solution was

added to the zinc and the flask was warmed until a reaction began. Stirring was begun and the rest of the solution was added at such a rate that gentle refluxing was maintained. The addition required one hour.

The reaction mixture was refluxed for an additional 30 minutes. The flask was then cooled in an ice bath and the contents were poured carefully into 300 ml of ice cold 5% sulfuric acid. The benzene layer was removed and washed once with 25 ml of cold 10% aqueous sodium carbonate, then with 25 ml of cold 5% sulfuric acid, and, finally, with two 25 ml portions of water. The combined acid extracts were washed with two 50 ml portions of ether, and the combined ether and benzene solutions dried with 5 g of anhydrous magnesium sulfate. After filtration, the solvent is removed by evaporation on a steam cone. No product was obtained.

Attempt to Synthesize the Antimony and Arsenic Analogs of Tribenzamide

A 200 ml three-neck round-bottom flask was fitted with a dropping funnel and an ice-water Friedrich condenser. The third neck was tightly stoppered with a ground glass stopper. A trap with a T-tube connection was placed in a pentane-Dry Ice bath and connected to the condenser by means of Tygon tubing; to the other part of the T-tube, a piece of Tygon tubing with a glass nozzle was attached. The nozzle was placed in an Erlenmeyer flask which contained a solution of 25% benzoyl chloride in dry pyridine. A magnetic stirring bar was placed in the three-neck reaction flask and a solution of 2 g lithium aluminum hydride in dry ether was placed in the flask. The reaction flask was cooled to 0°C by use of an ice-water bath and a magnetic stirrer was

placed under the ice bath. A solution of 0.5 g antimony trichloride in dry ether was placed in the dropping funnel and dropped slowly into the stirred lithium aluminum hydride solution.

The stibine which was generated was condensed in the pentane trap and was allowed to flow through the benzoyl chloride solution by lifting the trap out of the pentane bath. When bubbling ceased, the benzoyl chloride solution was poured into water in order to precipitate the tribenzoyl antimony. No product was obtained from this reaction.

Essentially the same procedure was followed in attempting to prepare the arsenic analog of tribenzamide without success.

SUMMARY

A study was made of some reactions of tribenzamide as a representative tertiary amide. Tribenzamide was found to react with Grignard reagents in much the same way that esters and primary amides do. With aromatic Grignard reagents, tertiary alcohols were obtained, but with aliphatic Grignard reagents, ketones were obtained.

Hydrazine and its derivatives might be expected to react with tertiary amides to yield interesting compounds. Since secondary amides react with hydrazine and substituted hydrazine to yield substituted triazoles[36], and diacetamide reacts with semicarbazide to yield a cyclic compound[36], there is reason to believe that tertiary amides could undergo similar reactions to yield ring compounds. It was found, however, that tertiary amides underwent hydrazinolysis to yield N,N-diaroylhydrazines.

A thorough study was made of the reduction of tribenzamide by the use of numerous methods of reduction. In all cases, the reduction product was N-benzylbenzamide, instead of the expected tribenzylamine. Benzyl alcohol was the other product obtained in these reductions. (Benzaldehyde was obtained when substituted lithium aluminum hydride was used as the reducing agent.)

A number of other reactions involving nucleophilic attack at the carbonyl carbon of tribenzamide were performed and the results are presented in this paper.

A major portion of this investigation was directed toward the determination of the structure of the tertiary amides and related compounds. Spectral data and most of the chemical evidence obtained in this investigation supported the pyramidal structure assigned to

tertiary amides. Some chemical evidence, such as the inability to quaternize tertiary amides, did not support the pyramidal structure. However, it is conceivable that quaternization might be made to proceed if different reaction conditions or different quaternizing reagents are used.

The results of an attempt to synthesize a bicyclic tertiary amide are also presented in this paper, as well as the results of an attempt to prepare the arsenic and antimony analogs of tribenzamide.

The chemistry of tertiary amides deserves further study. A number of other reagents such as isocyanides might be made to undergo reactions with tertiary amides. The reactions which have already been performed might be repeated using various reaction conditions, particularly the quaternization reactions. Recently[69], work has been performed on the quaternization of compounds using toluenesulfonyl perchlorate as the quaternizing agent. This reaction should be attempted with tertiary amides.

The pyrolysis of tertiary amides should be investigated further, with special emphasis being placed on the identification of the solid product obtained and a determination of the decomposition mechanism.

Attempts should be made to synthesize aliphatic tertiary amides, including triformamide, which is presently unknown. It seems likely that the aliphatic tertiary amide, triacrylamide, could be synthesized since tricinnamamide has been prepared. If triacrylamide could be synthesized, catalytic hydrogenation of this compound could lead to the saturated aliphatic tertiary amide.

REFERENCES

1. C. Noller, Chemistry of Organic Compounds, 1st Ed., Philadelphia, Saunders, 1954, p. 238.

2. C. Noller, Chemistry of Organic Compounds, 2nd Ed., Philadelphia, Saunders, 1957, p. 244.

3. T. Curtius, Ber., 23, 3041 (1890).

4. H. Wichelhaus, Ber., 3, 847 (1870).

5. W. Hentschell, Ber., 23, 2401 (1890).

6. R. L. Shriner, R. C. Fuson, and D. Y. Curtin, The Systematic Identification of Organic Compounds, 4th Ed., New York, John Wiley and Sons, Inc., 1956, p. 98.

7. Q. E. Thompson, J. Am. Chem. Soc., 73, 5841-46 (1958).

8. H. C. Brown and A. Tsukamoto, J. Am. Chem. Soc., 81, 502-3 (1959).

9. F. C. Whitmore, Organic Chemistry, 2nd Ed., D. van Nostrand and Co., New York, 1951, p. 415; E. E. Royals, Advanced Organic Chemistry, Prentice-Hall, Inc., New York, 1954, p. 619; V. Migrdichian, Organic Synthesis, Vol. I, Reinhold Publishing Corp., New York, 1957, p. 370.

10. J. N. Rakshit, J. Chem. Soc., 103, 1561 (1913).

11. N. V. Smirnova, A. P. Skoldinov, and J. A. Kocheskov, Doklady Akad. Nauk, 84, 737 (1952); Chem. Abstr., 47, 3233a (1953).

12. J. T. Bell, M.S. Thesis, Louisiana State University, 1965.

13. K. Brunner, Ber., 47, 2671 (1914).

14. M. Jaffe, J. Chem. Soc., 64, 29 (1893).

15. H. L. Wheeler, P. T. Walden, H. F. Metcalf, J. Chem. Soc., 74, 186 (1898).

16. C. Blacher, Ber., 28, 435 (1898).

17. A. E. Garrod and W. H. Hurtley, J. Physiol., 34, 217 (1910).

18. A. Ellinger and O. Riesser, Z. Physiol. Chem., 62, 271-5 (1910).

19. A. Parts, Z. Physik. Chem., 131, 405-8 (1938).

20. J. Yasumura, Sci. Papers Faculty Eng. Univ. Tokushima, 3, 14-19 (1951).

21. P. E. Koenig, J. M. Morris, P. S. Mason, and E. G. Blanchard, J. Org. Chem., 26, 4777 (1961).

22. W. V. Farrar, J. Chem. Soc., 3063-69 (1960), Part III.

23. N. Sharghi and I. Lalezari, J. Chem. Eng. Data, 10, 196 (1965).

24. R. Tyka and E. Plazek, Roczniki Chemü., 37, 283-91, 1151 (1963).

25. B. Witkop and J. B. Patrick, J. Am. Chem. Soc., 74, 3861 (1952).

26. K. Schreiber and V. Fernandez, J. Org. Chem., 26, 1744 (1961).

27. (a) K. Ieyoub, M.S. Thesis, Louisiana State University, 1965;

(b) R. P. Cowart, M.S. Thesis, Louisiana State University, 1965.

28. H. C. Brown and S. Rao, J. Am. Chem. Soc., 80, 5377 (1958).

29. L. I. Zakharkin and I. M. Khorlina, Izv. ANSSR Otd. Khimia, 2146 (1959).

30. L. I. Zakharkin and I. M. Khorlina, Izv. ANSSR Otd. Khimia, No. 3, 538 (1962).

31. H. C. Brown and B. C. Rao, J. Am. Chem. Soc., 82, 681 (1960).

32. H. C. Brown and P. Heim, ibid., 86, 3566 (1964).

33. S. W. Chaikin and W. G. Brown, ibid, 71, 122-5 (1949)

34. J. Dale, J. Chem. Soc., 910-22 (1961).

35. Z. Horü, C. Ievata, Y. Tamura, J. Org. Chem., 26, 2273-6 (1961).

36. K. Brunner, Monatsh., 36, 509, 514 (1915).

37. H. Wolchowe, Monatsh., 37, 480 (1916).

38. W. L. Mosby, J. Chem. Soc., 3997 (1957), Part III.

39. N. Maxim, Compt. rend., 182, 1393-95 (1926).

40. K. Heyns and W. Pyrus, Chem. Ber., 88, 678-683 (1955).

41. M. L. Bouveault, Bull. Soc. Chim., (3), 31, 1322-27 (1904).

42. V. Grignard and L. Tissier, Compt. rend., 132, 683-5 (1901); Chem. Zentr., I, 930 (1901).

43. M. S. Newman and A. S. Smith, J. Org. Chem., 13, 592-98 (1948).

44. A. Mustafa, W. Asker, O. H. Hishmat, A. F. A. Shalaby and M. Kamel, J. Am. Chem. Soc., 76, 5448 (1954).

45. V. Grignard, J. Chem. Soc., 80, I, 250 (1901).

46. M. S. Kharasch, Grignard Reactions of Nonmetallic Substances, New York, Prentice-Hall, Inc., 1954, p. 550.

47. E. Reid, Am. Chem. J., 41, 483 (1909).

48. R. T. Morrison and R. N. Boyd, Organic Chemistry, Boston, Allyn and Bacon, Inc., 1959, p. 480.

49. G. Labruto, Gazz. Chim. Ital., 63, 266-69 (1931).

50. L. Irrera, ibid, 65, 464-66 (1935).

51. J. D. Roberts and M. C. Caserio, Basic Principles of Organic Chemistry, W. A. Benjamin, Inc., New York, 1964, p. 674.

52. T. Uno and K. Machida, Bull. Chem. Soc. Japan, 34, 545 (1961).

53. R. N. Jones, J. Am. Chem. Soc., 67, 2127 (1945).

54. J. P. Jones, Unpublished work.

55. A. W. Titherly and W. L. Hicks, J. Chem. Soc., 89, 713 (1906).

56. J. H. Brewster, J. Am. Chem. Soc., 76, 6365 (1954).

57. M. H. Fournier, Bull. Soc. Chim., (3), 35, 14 (1906); (4), 7, 836-40 (1910).

58. M. S. Newman and W. T. Booth, J. Am. Chem. Soc., 67, 154 (1945).

59. W. C. LaCarna, Unpublished work.

60. R. Adams and E. H. Vollweiler, J. Am. Chem. Soc., 40, 1732-46 (1918).

61. F. A. Cotton and G. Wilkinson, Advanced Inorganic Chemistry, Interscience Publishers, 1962, p. 373.

62. A. I. Vogel, A Textbook of Practical Organic Chemistry, 3rd Ed., Longmans, Green, and Co., London, New York, Toronto, 1956, p. 258.

63. R. Adams, H. M. Chiles, C. F. Rassweiler, Organic Syntheses, Vol. V, New York, John Wiley and Sonc, Inc., 1925, pp. 5-6.

64. C. K. Ingold and L. C. Nickolls, J. Chem. Soc., 121, 1642 (1922).

65. R. Adams, H. M. Chiles, Organic Syntheses, Vol. V, New York, John Wiley and Sons, Inc., 1925 pp. 53-54.

66. L. Fieser, Experiments in Organic Chemistry, 3rd Ed., revised, D. C. Heath and Co., Boston, 1957, pp. 175-6.

67. R. Conner, J. Org. Chem., 3, 576 (1939).

68. Organic Reactions, Vol. I, New York, John Wiley and Sons, Inc., 1942, pp. 16-17

69. F. Klages and F. Malecki, Liebigs Ann. Chem., 691, 15 (1966).

VITA

Kalil Phillip Ieyoub, son of Mr. and Mrs. Phillip A. Ieyoub, was born in Lake Charles, Louisiana on August 21, 1935. He attended public elementary schools and graduated from Lake Charles High School in 1953.

In the fall of 1953, he entered McNeese State College where he began studies for a degree in chemistry. While at McNeese, he served as vice-president, then president of the Student Body, president of Blue Key National Honor Fraternity, and was listed in Who's Who in American Colleges and Universities. In June, 1958, he received his B.S. in Chemistry. After serving six months in the U.S. Infantry as a 2nd Lieutenant, he returned to McNeese where he was employed as a chemistry laboratory instructor for three years.

He entered the Graduate School of L.S.U. in Baton Rouge in 1962, and accepted a graduate teaching assistantship in chemistry.

While there, he served as vice-president of Phi Lambda Upsilon honorary chemical society. Mr. Ieyoub was the recipient of National Science Foundation and a Cities Service Corporation research grants. He received his M.S. degree in January, 1965.

He is married to the former Julie Christ of Lake Charles, and they have three children, Christopher Paul, age 5, Laura Ann, age 3, and Allison Claire, age 1.

Mr. Ieyoub is now a candidate for a Doctor of Philosophy Degree.

EXAMINATION AND THESIS REPORT

Candidate: Kalil Phillip Ieyoub

Major Field: Chemistry

Title of Thesis: The Chemistry of Tertiary Amides and Related Compounds

Approved:

Paul E. Peterson
Major Professor and Chairman

Max Goodrich
Dean of the Graduate School

EXAMINING COMMITTEE:

Virginia R. Williams

James D. Trayham

Joel Selbin

Date of Examination:

September 17, 1966